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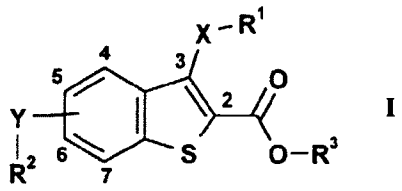
(54) Benzothiophene derivatives useful in therapy

(57) Compounds of formula I,



I

wherein

X represents O or $S(O)_m$;
R^1 and R^2 independently represent phenyl, naphthyl or heteroaryl; each of which is optionally fused and optionally substituted;
Y represents a bond, O, $(CH_2)_n$, $O(CH_2)_n$, $(CH_2)_nO$, or $CH(C_{1-6}alkyl)O$;
R^3 represents H or C_{1-6} alkyl;
m represents 0, 1, or 2; and
n represents 1, or 2;

and pharmaceutically acceptable salts thereof, are useful in therapy, in particular in the treatment of restenosis, renal failure and pulmonary hypertension.

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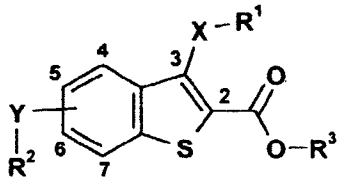
Description

[0001] This invention relates to benzo[b]thiophene-2-carboxylic acid derivatives useful in the treatment of a variety of diseases including restenosis, renal failure and pulmonary hypertension, and to pharmaceutical formulations containing such compounds.

[0002] Certain benzo[*b*]thiophene-2-carboxylic acids have been reported to have the ability to antagonise the effect of endothelin at the ET_A receptor while having a weaker effect at the ET_B receptor [Bioorg & Med Chem Letts *12*, p1367-1370, (1996)]. In particular, 5-benzyloxy-3-isopropoxybenzo[*b*]thiophene-2-carboxylic acid and 3-[(3-methoxyphenyl)sulfanyl] benzo[*b*]thiophene-2-carboxylic acid have an IC_{50} against the rabbit ET_A receptor of 6 and 5.9μM respectively. The former compound has an IC_{50} of 8.8μM against the human ET_A receptor. It was reported that the 1-position plays a role in receptor binding, and compounds of much greater affinity were obtained by replacement of the sulfur atom by N-(substituted benzyl) to give indole analogues (US 5,482,960). Furthermore, structure-activity studies in the resulting indole series indicated that methoxy substitution at the indole 5- and 6-positions was necessary for optimal potency. Replacement of the 6-methoxy with 6-benzyloxy was highly detrimental giving a ~1,000-fold reduction in potency (cf examples 21 and 22 in the Bioorg & Med Chem Letts reference).

[0003] Benzo[*b*]thiophene-2-carboxylic acid derivatives have also been indicated as inhibitors of thromboxane synthase (see EP 50957 and GB 2,118,552).

[0004] According to the present invention, there is provided a compound of formula I,



I

wherein

X represents O or $S(O)_m$;
R^1 and R^2 independently represent phenyl, naphthyl or heteroaryl containing 1, 2 or 3 heteroatoms independently selected from N, S and O; the ring being optionally fused to a saturated or unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms independently selected from N, S and O; the ring system as a whole being optionally substituted by one or more groups selected from OH, halogen, CN, NH_2, $(CH_3SO_2)HN$, $(CH_3SO_2)_2N$, C_{1-6} alkyl (optionally substituted by OH or CH_3CO_2) and C_{1-6} alkoxy;
Y represents a bond, O, $(CH_2)_n$, $O(CH_2)_n$, $(CH_2)_nO$, or $CH(C_{1-6}alkyl)O$;
R^3 represents H or C_{1-6} alkyl;
m represents 0, 1, or 2; and
n represents 1, or 2;

provided that:

(i) when R^2 is linked to Y via a nitrogen atom, then Y does not represent O, $O(CH_2)_n$ or CH_2O; and
(ii) when R^3 represents H, then neither R^1 nor R^2 is substituted by $(CH_3SO_2)_2N$; or a pharmaceutically acceptable salt thereof (referred to together herein as "the compounds of the invention").

[0005] The compounds excluded by the provisos are not sufficiently stable to be useful as drugs.

[0006] Groups that Y represents are written starting with the atom most remote from the benzo ring: for example "$O(CH_2)_n$" has R^2 attached to the oxygen atom and the benzo ring attached to a carbon atom.

[0007] Pharmaceutically acceptable salts include alkali metal salts (for example sodium salts) of any acidic groups that may be present, and acid addition salts (for example ammonium salts) of any basic groups that may be present.

[0008] "Halogen" includes fluorine, chlorine, bromine and iodine.

[0009] Alkyl groups which R^{1-3} and Y represent or comprise may be straight chain, branched or cyclic.

[0010] Specific heteroaryl groups that R^1 and R^2 may represent or comprise include pyridyl, pyrimidinyl, imidazolyl, thienyl, triazolyl, pyrazinyl, pyridazinyl and thiazolyl.

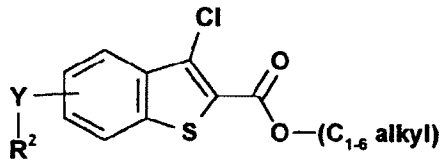
[0011] Preferred groups of compounds include those in which:

(a) X represents SO or S;

(b) R^1 represents phenyl or substituted phenyl, for example phenyl substituted by methoxy;
(c) R^2 represents 3-pyridyl, 5-pyrimidinyl, 1-imidazolyl, imidazo[4,5-c]pyridin-3-yl or 3-thienyl;
(d) Y represents CH_2, CH_2O or OCH_2;
(e) Y is attached to the 6-position of the benzothiophene ring;
(f) R^3 represents H; and
(g) a heteroatom in R^2 is separated from the benzothiophene ring by 4 atoms.

[0012] According to the invention, there is also provided a process for the production of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolysis of a compound of formula I in which R^3 represents C_{1-6} alkyl, to produce a corresponding compound of formula I in which R^3 represents H;
(b) oxidation of a compound of formula I in which X represents S and R^3 represents C_{1-6} alkyl, to produce a corresponding compound of formula I in which X represents SO or SO_2;
(c) when X represents S or O, reaction of a compound of formula II,

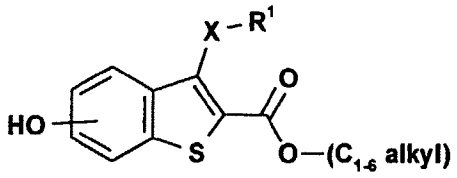


II

wherein Y and R^2 are as defined above, with a compound of formula III,

$$HX^aR^1 \qquad \text{III}$$

wherein R^1 is as defined above and X^a represents S or O, in the presence of a base;
(d) when Y represents $(CH_2)_nO$ or $CH(C_{1-6}$ alkyl)O, reaction of a compound of formula V,

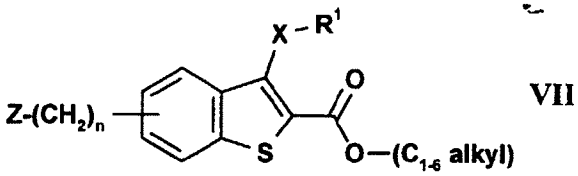


V

wherein X and R^1 are as defined above, with a compound of formula Va,

$$R^2Y^aZ \qquad \text{Va}$$

wherein R^2 is as defined above, Y^a represents $(CH_2)_n$ or $CH(C_{1-6}$ alkyl), and Z represents a leaving group or OH;
(e) when Y represents $O(CH_2)_n$, reaction of a compound of formula VII,



VII

wherein X, R^1 and n are as defined above, and Z is a leaving group, with a compound of formula VIIa,

$$R^2OH \qquad \text{VIIa}$$

wherein R^2 is as defined above, in the presence of a base;
(f) when Y represents $(CH_2)_n$ and R^2 represents N-linked heteroaryl, reaction of a compound of formula VII, as defined above, with a compound of formula VIIb.

$$R^{2a}H \qquad \text{VIIb}$$

wherein R^{2a} represents an N-containing heteroaromatic compound with a hydrogen atom attached to the N, in the presence of a base;

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable salt or vice versa.

[0013] In process (a), the hydrolysis may be carried out in a solvent which does not adversely affect the reaction (for example 1,4-dioxane or methanol) in the presence of a base (such as sodium hydroxide), at an elevated temperature.

[0014] In process (b), suitable oxidizing agents include hydrogen peroxide. The oxidation may be carried out in a solvent which does not adversely affect the reaction (for example acetic acid), at an elevated temperature. When producing a compound in which X represents SO, controlled oxidation using a stoichiometric amount of hydrogen peroxide, or sodium metaperiodate in aqueous methanol or acetic acid at a temperature ranging from ambient to reflux, is preferred.

[0015] In process (c), when X^a represents S, suitable bases include 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction may be carried out in a solvent which does not adversely affect the reaction (for example dimethylformamide), at a temperature of 20 - 100°C. When X^a represents O, similar conditions may be used, except that sodium hydride is a suitable base.

[0016] In process (d), suitable leaving groups that Z may represent include halogen (such as chloro), methanesulfonate and toluenesulfonate. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example dimethylformamide), at ambient temperature. Suitable bases include potassium carbonate. Alternatively, when Z represents OH, a Mitsunobu reaction may be performed using a phosphine and a dialkyldiazocarboxylate.

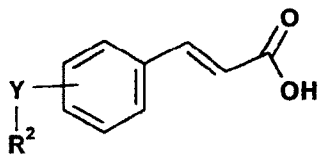
[0017] A process analogous to process (d) may also be used at an earlier stage in the synthesis on a compound analogous to compounds of formula V but in which XR^1 is replaced with Cl, to give a compound of formula II.

[0018] In process (e), suitable leaving groups that Z may represent include halogen (such as chloro), methanesulfonate and toluenesulfonate. The reaction may be carried out in a solvent which does not adversely affect the reaction (for example dimethylformamide), at ambient temperature. Suitable bases include sodium hydride and potassium carbonate.

[0019] A process analogous to process (d) may also be used at an earlier stage in the synthesis on a compound analogous to compounds of formula VII but in which XR^1 is replaced with Cl, to give a compound of formula II.

[0020] In process (f), suitable leaving groups that Z may represent include halogen (such as bromo). The reaction may be carried out in a solvent which does not adversely affect the reaction (for example dimethylformamide), around 0°C. Suitable bases include sodium hydride and potassium carbonate.

[0021] Compounds of formula II may be prepared from a propenoic acid of formula **IV**,

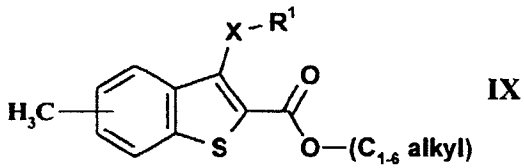


IV

wherein R^2 and Y are as defined above, by reaction with thionyl chloride followed by treatment of the resulting acid chloride with an alcohol to give the desired ester. The reaction with thionyl chloride is described in WO 95/15323 and by A J Krubsack and T Higa in Journal of Organic Chemistry 1976, 41(21), 3399-3403.

[0022] Compounds of formula V may be obtained from corresponding compounds of formula I in which R^2Y represents benzyloxy, by hydrogenation over a palladium catalyst in a solvent such as ethanol, or by treatment with trifluoroacetic acid in the precence of a carbonium scavenger such as thioanisole at ambient temperature.

[0023] Compounds of formula VII in which Z is a leaving group may be prepared from corresponding compounds of formula VII in which Z is OH by standard methods; for example, reaction with methanesulfonyl chloride in dichloromethane in the presence of a base such as triethylamine to give a compound in which Z is methanesulfonate. Alternatively, compounds of formula VII in which Z is Br or Cl and n is 1 may be prepared from corresponding compounds of formula IX,



IX

in which X and R^1 are as defined above, by reaction with N-bromosuccinimide or N-chlorosuccinimide in an inert solvent such as CCl_4.

[0024] Compounds of formula VII in which Z is OH and n is 2 may be prepared analogously to compounds of formula I, for example by starting with a compound analogous to a compound of formula IV in which R^2Y is replaced with benzyl-OCH_2CH_2, and then deprotecting the resulting compound by hydrogenolysis.

[0025] Compounds of formula VII in which Z is OH may be prepared from corresponding compounds of formula VII in which Z is Br or Cl, by treatment with sodium acetate to give compounds substituted by CH_3CO_2, followed by ester cleavage using potassium carbonate in ethanol.

[0026] Compounds of formula IX may be prepared analogously to compounds of formula I, for example starting with a compound analogous to a compound of formula IV but in which R^2Y is replaced with an appropriate alkyl group.

[0027] The intermediate compounds of formulae V and VII, as defined above, form a further aspect of the invention.

[0028] Compounds of formulae III, IV, Va, VIIa and VIIb are either known or are available using known techniques.

[0029] The compounds of the invention may be separated and purified by conventional methods.

[0030] It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of formula I. This may be achieved by conventional techniques, for example as described in 'Protective Groups in Organic Synthesis' by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991.

[0031] The compounds of formula I may possess one or more chiral centres and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present invention. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of formula I.

[0032] The compounds of formula I may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention.

[0033] The compounds of formula I are useful because they have pharmacological activity in animals, including humans. More particularly, they are useful in the treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, male erectile dysfunction, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia or cyclosporin induced nephrotoxicity. The treatment of restenosis, renal failure, pulmonary hypertension and male erectile dysfunction are of particular interest. The compounds of formula I may be administered alone or as part of a combination therapy. Treatment of companion animals such as dogs and cats is also contemplated.

[0034] Thus, according to a further aspect of the invention, there is provided a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

[0035] There is further provided a pharmaceutical formulation comprising a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

[0036] The invention also provides the use of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, male erectile dysfunction, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia or cyclosporin induced nephrotoxicity. The invention also provides a method of treatment of these diseases, which comprises administering a therapeutically effective amount of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.

[0037] Without being limited by theory, the compounds of formula I are believed to be endothelin receptor antagonists. Endothelin (ET) is a potent vasoconstrictor synthesised and released by endothelial cells. There are three distinct isoforms of ET: ET-1, ET-2 and ET-3, all being 21-amino acid peptides and herein the term 'endothelin' refers to any

or all of the isoforms. Two receptor subtypes, ET_A and ET_B have been pharmacologically defined (see for example H. Arai et al, *Nature,* **348,** 730 , 1990) and further subtypes have recently been reported. Stimulation of ET_A promotes vasoconstriction and stimulation of ET_B receptors causes either vasodilation or vasoconstriction.

[0038] The effects of endothelin are often long-lasting and, as the endothelins are widely distributed in mammalian tissues, a wide range of biological responses has been observed in both vascular and non-vascular tissue. The main effects of endothelin are observed in the cardiovascular system, particularly in the coronary, renal, cerebral and mesenteric circulation.

[0039] Increased circulating levels of endothelin have been observed in patients who have undergone percutaneous transluminal coronary angioplasty (PTCA) (A.Tahara et al, *Metab. Clin. Exp.* **40**, 1235, 1991) and ET-1 has been found to potentiate neointimal formation in rats after balloon angioplasty (S.Douglas et al, *J.Cardiovasc.Pharm.,* **22** (Suppl 8), 371, 1993). The same workers have found that an endothelin antagonist, SB-209670, causes a 50% reduction in neointimal formation relative to control animals (S.Douglas et al, *Circ Res,* 75, 1994). Antagonists of the endothelin receptor may thus be useful in preventing restenosis post PTCA.

[0040] Endothelin-1 is produced in the human prostate gland and endothelin receptors have been identified in this tissue. Since endothelin is a contractile and proliferative agent endothelin antagonists could be useful in the treatment of benign prostate hypertrophy.

[0041] There is widespread localisation of endothelin and its receptors in the central nervous system and cerebrovascular system (R.K.Nikolov et al, *Drugs of Today,* **28**(5), 303, 1992) with ET being implicated in cerebral vasospasm, cerebral infarcts and neuronal death. Elevated levels of endothelin have also been observed in patients with:

- Chronic renal failure (F.Stockenhuber et al, *Clin Sci* (Lond.), **82**, 255, 1992)
- Ischaemic Heart Disease (M.Yasuda, *Am. Heart J.,* **119**, 801, 1990)
- Stable or unstable angina (J.T.Stewart, *Br. Heart J.* **66**, 7 1991)
- Pulmonary Hypertension (D.J.Stewart et al, *Ann. Internal Medicine,* **114,** 464, 1991)
- Congestive heart failure (R.J.Rodeheffer et al, *Am.J.Hypertension,* **4**, 9A, 1991)
- Preeclampsia (B.A.Clark et al, *Am.J.Obstet. Gynecol.,* **166**, 962, 1992)
- Diabetes (A.Collier et al, *Diabetes Care,* **15** (8), 1038, 1992)
- Crohn's disease (S.H.Murch et al, *Lancet,* **339**, 381, 1992)
- Atherosclerosis (A.Lerman et al, *New Eng. J. Med.,* **325**, 997, 1991)

[0042] In every case the disease state associated with the physiologically elevated levels of endothelin is potentially treatable with an endothelin receptor antagonist and hence a compound of formula I.

[0043] Compounds that selectively antagonise the ET_A receptor rather than the ET_B receptor are preferred.

[0044] The biological activity of the compounds of formula I may be demonstrated in Tests A-C below:

A. Binding assay

[0045] Competition between test compounds and ^{125}I-ET-1 binding to human endothelin receptors is determined as follows.

Binding to ET_A receptors

[0046] 25µl of a 30pM solution of [^{125}I]Tyr^{13} ET-1 (specific activity 2,200Ci/mM) is mixed with 25µl samples of test compound (final concentrations in the range 0.1nM - 50,000nM). 200µl of a solution containing cloned human ET_A receptor (0.75pmoles receptor protein/ml), 50mM Tris, 0.5mM $CaCl_2$, 0.1% human serum albumen, 0.1% bacitracin, 0.05% Tween 20, pH 7.4 is added. The solution is mixed at 37°C for 2 hours. After the incubation, the unbound ligand is separated from receptor bound ligand by filtration with a Brandel cell harvester, followed by three washes of buffer. Filter papers are counted for radioactivity, and the IC_{50} (the concentration of test compound at which 50% of the radiolabelled compound is unbound) determined for the concentration range tested.

Binding to ET_B receptors

[0047] 25µl of a 30pM solution of [^{125}I]Tyr^{13} ET-1 (specific activity 2,200Ci/mM) is mixed with 25µl samples of test compound (final concentration 0.1nM - 50,000nM). 200µl of a solution containing cloned human ET_B receptor (0.25pmoles receptor protein/ml), 50mM Tris, 0.5mM $CaCl_2$, 0.1% human serum albumen, 0.1% bacitracin, 0.05% Tween 20, pH 7.4 is added. The solution is mixed at 37°C for 2 hours. After the incubation, the unbound ligand is separated from receptor bound ligand by filtration with a Brandel cell harvester, followed by three washes of buffer. Filter papers are counted for radio-activity, and the IC_{50} (the concentration of test compound at which 50% of the radio-

labelled compound is unbound) determined for the concentration range tested.

B. *In vitro* vascular smooth muscle activity

Rat aorta

[0048] Rat aortae are cleaned of connective tissue and fat and cut into helical strips approx 4mm in width. The endothelium is removed by dragging the luminal surface of the tissue gently across filter paper moistened with Krebs solution of composition (mM) NaCl 130, KCl 5.6, $NaHCO_3$ 25, Glucose 11.1, NaH_2PO_4 0.6, $CaCl_2$ 2.16, $MgCl_2$ 0.5, gassed with 95% O_2/5% CO_2. The strips are mounted in isolated organ baths in Krebs solution under a resting tension of 1 gram. Organ bath solutions are maintained at 37°C and continuously aerated with 95% O_2/5% CO_2. Tensions are measured with Maywood Industries isometric force transducers and displayed on Gould TA4000 recorders. After equilibration in the organ bath for 1 hour, tissues are contracted by the addition of KCl to a final concentration of 60mM. The KCl is removed by replacing the Krebs solution, with two further washes with Krebs solution. To determine the potency of an ET_A receptor antagonist, two tissues are cumulatively dosed with ET-1 (0.1nM - 1 μM); other tissues are dosed with ET-1 (0.1nM-1μM) in duplicate, beginning 30 minutes after the inclusion in the organ bath medium of the test compound. Sufficient tissues are used per experiment to generate dose-response curves to ET-1 in the absence and the presence of at least 3 concentrations of antagonist. Data are expressed as the mean ± s.e.m. Dissociation constants (k_b) of competitive antagonists are calculated by the method of Arunlakshana and Schild.

Rabbit pulmonary artery

[0049] Isolated rabbit pulmonary arteries are cleaned of connective tissue and fat and cut into rings approx 4mm in width. The endothelium is removed by inserting a fibrous instrument moistened with Krebs solution of composition (mM) NaCl 130, KCl 5.6, $NaHCO_3$ 25, Glucose 11.1, NaH_2PO_4 0.6, $CaCl_2$ 2.16, $MgCl_2$ 0.5, gassed with 95% O_2/5% CO_2. The rings are mounted in isolated organ baths in Krebs solution under a resting tension of 1 gram. Organ bath solutions are maintained at 37°C and continuously aerated with 95% O_2/5% CO_2. Tensions are measured with Maywood Industries isometric force transducers and displayed on Gould TA4000 recorders. After equilibration in the organ bath for 1 hour, tissues are contracted by the addition of KCl to a final concentration of 60mM. The KCl is removed by replacing the Krebs solution, with two further washes with Krebs solution. To determine the potency of an ET_B receptor antagonist, two tissues are cumulatively treated with BQ-3020 (0.1nM - 1 μM); other tissues are treated with BQ-3020 (0.1nM - 1μM) in duplicate, beginning 30 minutes after the inclusion in the organ bath medium of the test compound. Sufficient tissues are used per experiment to generate dose-response curves to BQ-3020 in the absence and the presence of at least 3 concentrations of antagonist. Data are expressed as the mean ± s.e.m. Dissociation constants (k_b) of competitive antagonists are calculated by the method of Arunlakshana and Schild.

C. *In vivo* blockade of endothelin-induced blood pressure elevation

[0050] In anaesthetised, ganglion-blocked and artificially respired rats, the left common carotid artery and the right jugular vein are cannulated for the measurement of arterial blood pressure and the administration of compound respectively. Rats are treated with the ET_B antagonist BQ-788 (0.25mg/kg i.v.). Beginning 10 minutes after administering BQ-788, the hypertensive response to ET-1 (1μg/kg i.v.) is determined. When the blood pressure has returned to baseline, the test compound is administered (0.1 - 20mg/kg i.v.) and after 10 minutes the ET-1 challenge is repeated. Increasing concentrations of the test compound are administered, followed 10 minutes after each administration by a further ET-1 challenge. An IC_{50} is determined based upon inhibition of ET-1 induced pressor response upon cumulative dosing with compound.

[0051] Duration of blockade is determined in anaesthetised, ganglion-blocked and artificially respired rats, in which the left common carotid artery and the right jugular vein are cannulated for the measurement of arterial blood pressure and the administration of compound respectively. Rats are treated with the ET_B antagonist BQ-788 (0.25mg/kg i.v.). Beginning 10 minutes after administering BQ-788, the hypertensive response to ET-1 (1μg/kg i.v.) is determined. When the blood pressure has returned to baseline, the test compound is administered (10mg/kg i.v.). Further administrations of ET-1 are made 5, 20 and 60 minutes after dosing the test compound. In separate animals, prepared similarly, an ET-1 challenge is made 2 or 4 hours after dosing with the test compound, in these animals BQ-788 is dosed 10 minutes before the ET-1 challenge. For later time points, rats are dosed with the test compound (10mg/kg) i.v. *via* a tail vein or p.o., they are then anaesthetised and prepared for blood pressure measurement as above. In these rats, ET-1 (1μg/kg i.v.) was administered 6 or 8 hours after the test compound.

[0052] For human use the compounds of formula I can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard

pharmaceutical practice. For example they can be administered orally in the form of tablets containing such excipients as starch or lactose or in capsules or ovules either alone or in admixture with excipients or in the form of elixirs, solutions or suspensions containing the compound or salt in a liquid carrier, for example a vegetable oil, glycerine or water with a flavouring or colouring agent. They can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parental administration, they are best used as sterile aqueous solutions which may contain other substances, for example, enough glucose or salts to make the solution isotonic with blood. For parenteral administration the compound or salt may also be administered as a solution or suspension in a suitable oil, for example polyethylene glycol, lecithin or sesame oil.

[0053] Compounds of formula I may also be administered through inhalation of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane.

[0054] For oral or parenteral administration to human patients the daily dosage levels of compounds of formula I will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 5 mg/kg. Thus tablets will contain 1mg to 0.4g of compound for administration singly or two or more at a time, as appropriate. The above dosages are, of course only exemplary of the average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention.

[0055] Alternatively the compounds of formula I can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder or in the form of a medicated plaster, patch or membrane. For example they may be incorporated in a cream containing an aqueous emulsion of polyethylene glycols or liquid paraffin. The compounds may also be administered intranasally.

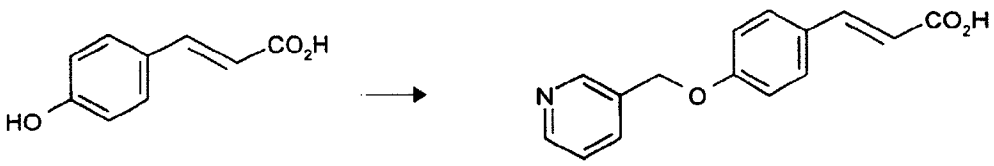
[0056] The invention is illustrated by the following Preparations and Examples, in which the following abbreviations may be used:

LRMS low resolution mass spectroscopy
NMR nuclear magnetic resonance
nOe nuclear Overhauser effect

Preparation 1

(*E*)-3-[4-(3-Pyridylmethoxy)phenyl]-2-propenoic acid

[0057]



[0058] An aqueous solution of 2M NaOH (165ml) was added to a solution of (*E*)-3-[4-hydroxyphenyl]-2-propenoic acid (16.4g, 100mmol) in ethanol (100ml). The mixture was stirred for 10 minutes, and then 3-(chloromethyl)-pyridine hydrochloride (19.7g, 120mmol) was added in portions. The mixture was stirred for 20 hours, and the solvents were evaporated under reduced pressure. Water was added and the suspension heated to give a solution. To this solution was added acetic acid, and the resultant precipitate was filtered and recrystallised from methanol to give the title compound as a colourless solid (15.6g).

m.p. 228-230°C

LRMS (Thermospray): 256.3 (MH^+)

^{1}H NMR (300MHz, DMSO-d_6): δ = 5.20 (s, 2H), 6.38 (d, 1H), 7.06 (d, 2H), 7.43 (m, 1H), 7.53 (d, 1H), 7.65 (d, 2H), 7.88 (d, 1H), 8.55 (d, 1H), 8.68 (s, 1H), 12.30 (brs, 1H).

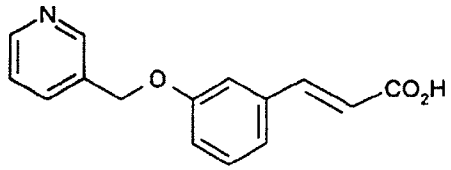
Analysis: Found: C, 70.25; H, 5.10; N, 5.43.

$C_{15}H_{13}NO_3$ Requires: C, 70.57; H, 5.13; N, 5.49.

Preparation 2

(*E*)-3-[3-(3-Pyridylmethoxy)phenyl]-2-propenoic acid

[0059]

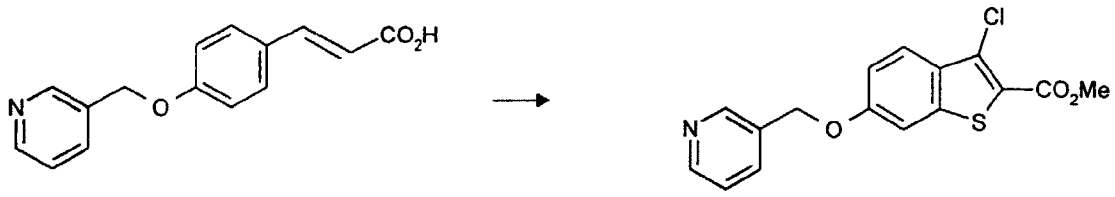


[0060] This was prepared by the same procedure as described for Preparation 1, using (*E*)-3-[3-hydroxyphenyl]-2-propenoic acid.
m.p. 169-171°C
LRMS (Thermospray): 256.2 (MH^+)
^{1}H NMR (300MHz, DMSO-d_6): δ = 5.20 (s, 2H), 6.58 (d, 1H), 7.06 (d, 1H), 7.23-7.47 (m, 4H), 7.55 (d, 1H), 7.88 (d, 1H), 8.55 (d, 1H), 8.70 (s, 1H), 12.50 (brs, 1H).
Analysis: Found: C, 70.05; H, 5.08; N, 5.47.
$C_{15}H_{13}NO_3$ Requires: C, 70.57; H, 5.13; N, 5.49.

Preparation 3

Methyl 3-chloro-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0061]

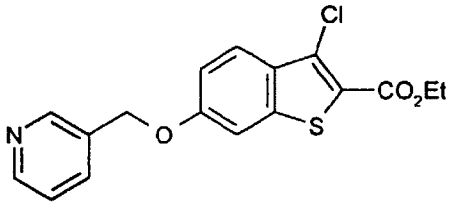


[0062] Thionyl chloride (0.72ml, 10mmol) was added dropwise to a stirred suspension of (*E*)-3-[4-(3-Pyridylmethoxy) phenyl]-2-propenoic acid (Preparation 1, 510mg, 2mmol) in chlorobenzene (3ml). The mixture was stirred at ambient temperature for 15 minutes, and then heated at reflux for 3 hours. The reaction mixture was cooled and dimethylformamide (0.15ml, 2mmol), and an additional portion of thionyl chloride (0.29ml, 4mmol), were added. The mixture was heated at reflux for a further 3 hours before being cooled and poured into methanol (20ml). The mixture was heated to reflux for 10 minutes, and after cooling, the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, and the organic layer separated, dried (magnesium sulfate) and evaporated under vacuo. The residue was flash chromatographed on silica gel using diethyl ether as eluant, and the product crystallised from diethyl ether and hexane to give the title compound as a colourless solid (310mg).
m.p. 148-150°C
LRMS (Thermospray): 334.3 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 3.95 (s, 3H), 5.18 (s, 2H), 7.19 (d, 1H), 7.30-7.38 (m, 2H), 7.79 (d, 1H), 7.88 (d, 1H), 8.61 (d, 1H), 8.73 (s, 1H).
Analysis: Found: C, 57.45; H, 3.53; N, 4.14.
$C_{16}H_{12}ClNO_3S$ Requires: C, 57.57; H, 3.62; N, 4.20.
[0063] Preparations 4-9 were prepared similarly using a 3-[(substituted)phenyl]-2-propenoic acids as described above, or 3-[(substituted)phenyl]-2-propenoic acids from commercial or literature sources. The ethyl esters are obtained by substituting ethanol for methanol.

Preparation 4

Ethyl 3-chloro-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0064]

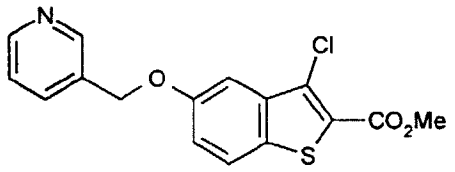


[0065] This was prepared by the same procedure as described for Preparation 3, with ethanol instead of methanol.
LRMS (Thermospray): 347.9 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.42 (q, 2H), 5.18 (s, 2H), 7.19 (d, 1H), 7.30-7.38 (m, 2H), 7.80 (d, 1H), 7.88 (d, 1H), 8.62 (d, 1H), 8.73 (s, 1H).
$C_{17}H_{14}ClNO_3S$.

Preparation 5

Methyl 3-chloro-5-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0066]

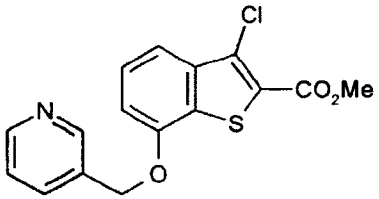


[0067] Thionyl chloride (20.3ml, 279mmol) was added slowly to a stirred suspension of (*E*)-3-[3-(3-Pyridylmethoxy) phenyl]-2-propenoic acid (Preparation 2, 14.2mg, 55.7mmol) in chlorobenzene (75ml). The mixture was then heated at reflux for 6 hours before being cooled and poured into methanol (1000ml). The mixture was heated to reflux for 30 minutes, and after cooling, the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, and the organic layer separated, dried (magnesium sulfate) and evaporated under vacuo. The residue was flash chromatographed on silica gel using a mixture of 90% diethyl ether, and 10% dichloromethane as eluant. The less polar product (first isomer eluted from the chromatography column) was crystallised from diethyl ether to give the title compound as a colourless solid (6.88g).
m.p. 126-128°C
LRMS (APCI): 334.8 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 3.98 (s, 3H), 5.21 (s, 2H), 7.23 (dd, 1H), 7.37 (dd, 1H), 7.45 (d, 1H), 7.71 (d, 1H), 7.83 (d, 1H), 8.63 (d, 1H), 8.76 (s, 1H).
Analysis: Found: C, 57.52; H, 3.57; N, 4.10.
$C_{16}H_{12}ClNO_3S$ Requires: C, 57.57; H, 3.62; N, 4.20.

Preparation 6

Methyl 3-chloro-7-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0068]

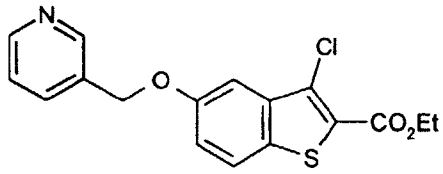


[0069] The more polar isomer from the formation of Preparation 5 was isolated by continuation of the flash chromatography to give this title compound which was crystallised from a dichloromethane and hexane mixture to give a colourless solid (2.42g).
m.p. 144-146°C
LRMS (APCI): 334.8 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 3.98 (s, 3H), 5.31 (s, 2H), 7.00 (d, 1H), 7.37 (dd, 1H), 7.45 (t, 1H), 7.62 (d, 1H), 7.85 (d, 1H), 8.63 (d, 1H), 8.76 (s, 1H).
Analysis: Found: C, 56.93; H, 3.56; N, 4.00.
$C_{16}H_{12}ClNO_3S$ Requires: C, 57.57; H, 3.62; N, 4.20.

Preparation 7

Ethyl 3-chloro-5-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0070]

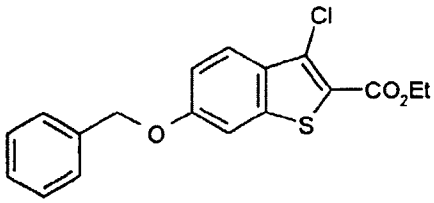


[0071] This was prepared by the same procedure as described for Preparation 5, with ethanol instead of methanol.
LRMS (Thermospray): 348.1 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.44 (t, 3H), 4.43 (q, 2H), 5.21 (s, 2H), 7.23 (dd, 1H), 7.37 (dd, 1H), 7.45 (d, 1H), 7.71 (d, 1H), 7.83 (d, 1H), 8.63 (d, 1H), 8.76 (s, 1H).
$C_{17}H_{14}ClNO_3S$.

Preparation 8

Ethyl 6-(benzyloxy)-3-chlorobenzo[*b*]thiophene-2-carboxylate

[0072]

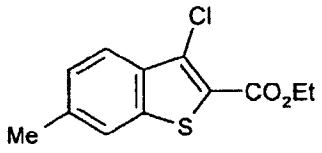


[0073] Thionyl chloride (7.3ml, 100mmol) was added slowly to a stirred mixture of (*E*)-3-[4-(benzyloxy)phenyl]-2-propenoic acid (5.08mg, 20mmol), pyridine (0.32ml, 4mmol) and dimethylformamide (1.5ml, 20mmol) in chlorobenzene (20ml). The mixture was then heated at 130°C for 24 hours, before being cooled and poured into ethanol (100ml). The mixture was heated briefly to reflux for 20 minutes and, after cooling, the solvents were removed under reduced pressure. The residue was partitioned between dichloromethane and aqueous ammonium hydroxide solution, and the organic layer separated, dried (magnesium sulfate) and evaporated under vacuo. The residue was flash chromatographed on silica gel using a mixture of 70% hexane and 30% dichloromethane as eluant, and the product was crystallised from diisopropyl ether to give the title compound as a colourless solid (930mg).
m.p. 98-100°C
LRMS (Thermospray): 347.0 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.41 (q, 2H), 5.17 (s, 2H), 7.18 (dd, 1H), 7.28-7.50 (m, 6H), 7.86 (d, 1H).
Analysis: Found: C, 62.14; H, 4.33.
$C_{18}H_{15}ClO_3S$ Requires: C, 62.33; H, 4.36.

Preparation 9

Ethyl 3-chloro-6-methylbenzo[*b*]thiophene-2-carboxylate

[0074]

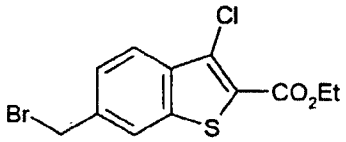


[0075] This was prepared by the same procedure as described for Preparation 8, and the product was crystallised from a diethyl ether and hexane mixture.
m.p. 66-68°C
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 2.50 (s, 3H), 4.42 (q, 2H), 7.31 (d, 1H), 7.60 (s, 1H), 7.85 (d, 1H).
Analysis: Found: C, 56.40; H, 4.31.
$C_{12}H_{11}ClO_2S$ Requires: C, 56.58; H, 4.35.

Preparation 10

Ethyl 6-bromomethyl-3-chlorobenzo[*b*]thiophene-2-carboxylate

[0076]

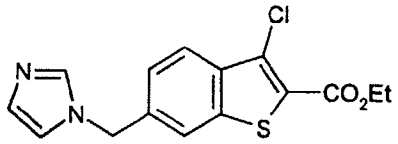


[0077] Catalytic azobisisobutylnitrile (AIBN, 0.28g) and N-bromosuccinimide (4.8g, 26.8mmol) were added to a solution of ethyl 3-chloro-6-methylbenzo[*b*]thiophene-2-carboxylate (Preparation 9, 6.5g, 25.5mmol) in tetrachloromethane (50ml), under a nitrogen atmosphere. The mixture was heated to reflux for 5 hours, cooled, and then loaded onto a silica gel column. The product was eluted with a gradient mixture of dichloromethane and hexane (initially 30:70 increasing to 50:50, and then 70:30). The solvent was removed under reduced pressure to leave the title compound as a colourless solid (8.7g)
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.42 (q, 2H), 4.61 (s, 2H), 7.50 (d, 1H), 7.82 (s, 1H), 7.93 (d, 1H).
$C_{12}H_{10}BrClO_2S$

Preparation 11

Ethyl 3-chloro-6-(1*H*-1-imidazolylmethyl)benzo[*b*]thiophene-2-carboxylate

[0078]



[0079] Imidazole (2.0g, 30mmol) was added in portions to a stirred suspension of sodium hydride (0.48g of 60% dispersion in mineral oil, 12mmol) in anhydrous dimethylformamide (15ml) at 0°C, under a nitrogen atmosphere. After 40 minutes, ethyl 6-bromomethyl-3-chlorobenzo[*b*]thiophene-2-carboxylate (Preparation 10, 3.33g, 10mmol) was added. After 2 hours the mixture was partitioned between ethyl acetate and water. The organic layer was separated and washed with more water, dried (magnesium sulfate), and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using 5% methanol in dichloromethane as eluant, and the isolated product was crystallised from diethyl ether to give the title compound as a colourless solid (2.02g).

m.p. 127-129°C

LRMS (Thermospray): 321.1 (MH^+)

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.42 (q, 2H), 5.28 (s, 2H), 6.93 (s, 1H), 7.13 (s, 1H), 7.28 (d, 1H), 7.54 (s, 1H), 7.62 (s, 1H), 7.93 (d, 1H).

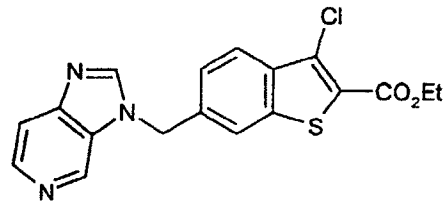
Analysis: Found: C, 55.75; H, 4.02; N, 8.61.

$C_{15}H_{13}ClN_2O_2S$ Requires: C, 56.16; H, 4.08; N, 8.73.

Preparation 12

Ethyl 3-chloro-6-(3*H*-imidazo[4,5-*c*]pyridin-3-ylmethyl)benzo[*b*]thiophene-2-carboxylate

[0080]



[0081] 1*H*-Imidazo[4,5-*c*]pyridine (536mg, 4.5mmol) was added in portions to a stirred suspension of sodium hydride (144mg of 60% dispersion in mineral oil, 3.6mmol) in anhydrous dimethylformamide (5ml) at 0°C, under a nitrogen atmosphere. After 40 minutes, ethyl 6-bromomethyl-3-chlorobenzo[*b*]thiophene-2-carboxylate (Preparation 10, 1g, 3mmol) was added. After 20 hours the mixture was partitioned between ethyl acetate and water. The organic layer was separated and washed with more water, dried (magnesium sulfate), and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using 5% methanol in dichloromethane as eluant. The fractions containing the less polar product (first isomer eluted from the chromatography column) were evaporated under reduced pressure to give the title compound as a colourless solid (160mg).

LRMS (Thermospray): 372.5 (MH^+)

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.42 (q, 2H), 5.60 (s, 2H), 7.35 (d, 1H), 7.64 (s, 1H), 7.76 (d, 1H), 7.97 (d, 1H), 8.12 (s, 1H), 8.50 (d, 1H), 8.75 (s, 1H).

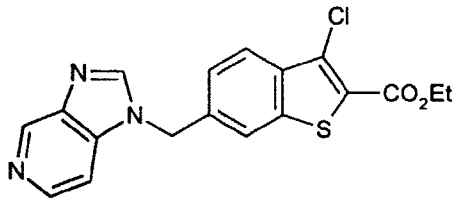
The regiochemistry of this isomer was confirmed by an observed nOe difference spectra between the 4-proton of the 3*H*-imidazo[4,5-*c*]pyridin-3-yl group, and the CH_2 link. In contrast, the isomer in Preparation 13 displayed an nOe between the 7-proton of the 1*H*-imidazo[4,5-*c*]pyridin-3-yl group, and the CH_2 linker.

$C_{18}H_{14}ClN_3O_2S$.

Preparation 13

Ethyl 3-chloro-6-(1*H*-imidazo[4,5-*c*]pyridin-1-ylmethyl)benzo[*b*]thiophene-2-carboxylate

[0082]

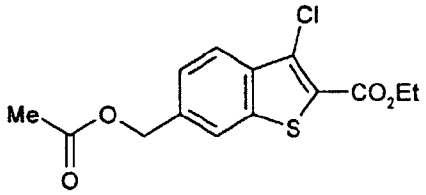


[0083] The more polar isomer from the formation of Preparation 12 was isolated by continuation of the flash chromatography to give this title compound as a colourless solid (230mg).
LRMS (Thermospray): 372.3 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.41 (t, 3H), 4.42 (q, 2H), 5.51 (s, 2H), 7.22 (d, 1H), 7.33 (d, 1H), 7.58 (s, 1H), 7.97 (d, 1H), 8.04 (s, 1H), 8.42 (d, 1H), 9.18 (s, 1H).
$C_{18}H_{14}ClN_3O_2S$.

Preparation 14

Ethyl 3-chloro-6-[(methylcarbonyloxy)methyl]benzo[*b*]thiophene-2-carboxylate

[0084]

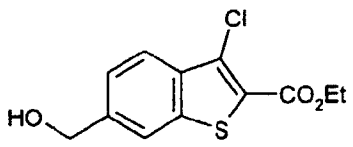


[0085] Sodium acetate (3.3g, 40.5mmol) was added to a stirred solution of ethyl 6-bromomethyl-3-chlorobenzo[b]thiophene-2-carboxylate (Preparation 10, 4.5g, 13.5mmol) in a mixture of anhydrous dimethylformamide (20ml) and anhydrous tetrahydrofuran (10ml), under a nitrogen atmosphere. The mixture was heated at 80°C for 20 hours, then the mixture was partitioned between diethyl ether and water. The organic layer was separated and washed with more water, dried (magnesium sulfate), and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using dichloromethane as eluant to give the title compound as a colourless gum (2.66g).
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 2.13 (s, 3H), 4.42 (q, 2H), 5.23 (s, 2H), 7.48 (d, 1H), 7.81 (s, 1H), 7.96 (d, 1H).
$C_{14}H_{13}ClO_4S$.

Preparation 15

Ethyl 3-(chloro)-6-(hydroxymethyl)benzo[*b*]thiophene-2-carboxylate

[0086]



[0087] Potassium carbonate (2g) was added to a stirred solution of ethyl 3-chloro-6-[(methylcarbonyloxy)methyl]benzo[b]thiophene-2-carboxylate (Preparation 14, 2.65g, 8.5mmol) in ethanol (40ml). The mixture was stirred at am-

bient temperature for 20 hours, then the solvent was removed under reduced pressure. The residue was partitioned between dichloromethane and water. The organic layer was separated and washed with more water, dried (magnesium sulfate), and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using a gradient of 0-2% methanol in dichloromethane as eluant to give the title compound, which was crystallised from diethyl ether to give a colourless solid(1.66g).

m.p. 117-118°C

LRMS (APCI): 270.4 (MH^+)

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 1.90 (brs, 1H), 4.42 (q, 2H), 4.88 (s, 2H), 7.47 (d, 1H), 7.83 (s, 1H), 7.95 (d, 1H).

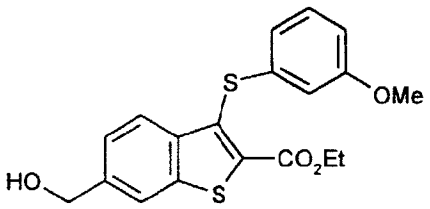
Analysis: Found: C, 52.95; H, 4.02.

$C_{12}H_{11}ClO_3S$ Requires: C, 53.24; H, 4.10.

Preparation 16

Ethyl 6-(hydroxymethyl)-3-[(3-methoxyphenyl)sulfanyl)benzo[*b*]thiophene-2-carboxylate

[0088]



[0089] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU - 1.1 ml, 7.23mmol) was added to a mixture of ethyl 3-(chloro)-6-(hydroxymethyl)benzo[*b*]thiophene-2-carboxylate (Preparation 15 - 1.63g, 6.02mmol) and 3-methoxybenzenethiol (1.1ml, 9.03mmol) in anhydrous dimethylformamide (8ml) under a nitrogen atmosphere. The solution was stirred at ambient temperature for 18 hours, and then heated to 60°C for 3 hours. The solution was partitioned between diethyl ether and water. The organics were separated and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residue was crystallised from diethyl ether and hexane to give the title compound as a colourless solid (1.77g).

m.p. 110-112°C

LRMS (Thermospray): 375.1 (MH^+)

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.37 (t, 3H), 1.80 (t, 1H), 3.69 (s, 3H), 4.39 (q, 2H), 4.81 (d, 2H), 6.63-6.76 (m, 3H), 7.10 (t, 1H), 7.32 (d, 1H), 7.80 (d, 1H), 7.88 (s, 1H).

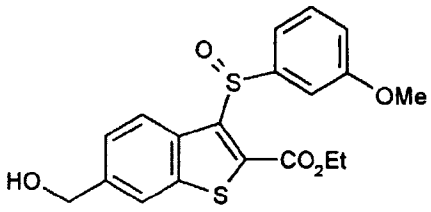
Analysis: Found: C, 60.66; H, 4.85.

$C_{19}H_{18}O_4S_2$ Requires: C, 60.94; H, 4.85.

Preparation 17

Ethyl 6-(hydroxymethyl)-3-[(3-methoxyphenyl)sulfinyl]benzo[*b*]thiophene-2-carboxylate

[0090]



[0091] Hydrogen peroxide in water (0.52ml of 30%w/v, 4.6mmol) was added to a solution of ethyl 6-(hydroxymethyl)-

3-[(3-methoxyphenyl)sulfanyl]benzo[*b*]thiophene-2-carboxylate (Preparation 16, 1.73g, 4.6mmol) in a mixture of acetic acid (20ml) and ethanol (10ml). The mixture was heated to 100°C for 60 minutes. The solvents were removed by evaporation under reduced pressure, and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was separated, dried (magnesium sulfate) and concentrated under vacuo, and the residue was flash chromatographed on silica gel using 2% ethanol in dichloromethane as eluant. The title compound was isolated as a foam (1.28g).

LRMS (Thermospray): 391.0 (MH^+)

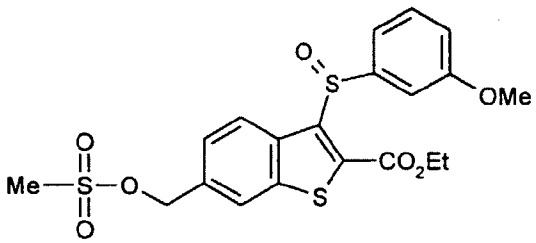
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 1.85 (t, 1H), 3.80 (s, 3H), 4.48 (q, 2H), 4.89 (d, 2H), 6.90 (d, 1H), 7.25-7.41 (m, 3H), 7.50 (s, 1H), 7.82 (s, 1H), 8.72 (d, 1H).

$C_{19}H_{18}O_5S_2$

Preparation 18

Ethyl 3-[(3-methoxyphenyl)sulfinyl)]-6-[(methylsulfonyloxy)methyl]-benzo[*b*]thiophene-2-carboxylate

[0092]



[0093] Methanesulfonyl chloride (0.043ml, 0.55mmol) was added to a stirred solution of ethyl 6-(hydroxymethyl)-3-[(3-methoxyphenyl)sulfinyl]benzo[*b*]thiophene-2-carboxylate (Preparation 17, 195mg, 0.5mmol) and *N*-ethyl-*N,N*-diisopropylamine (0.1ml, 0.55mmol) in dichloromethane (3ml) at 0°C. After 3 hours the solution was washed twice with water, dried (magnesium sulfate), and the solvent removed under reduced pressure. The residue was crystallised from diethyl ether to give the title compound as a colourless solid (155mg).

m.p. 80-83°C

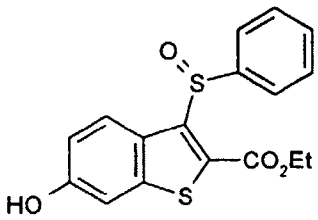
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.45 (t, 3H), 2.96 (s, 3H), 3.81 (s, 3H), 4.50 (q, 2H), 5.32 (s, 2H), 6.93 (dd, 1H), 7.30-7.43 (m, 3H), 7.50 (s, 1H), 7.88 (s, 1H), 8.80 (d, 1H).

$C_{20}H_{20}O_7S_3$

Preparation 19

Ethyl 6-(hydroxy)-3-(phenylsulfinyl)benzo[*b*]thiophene-2-carboxylate

[0094]



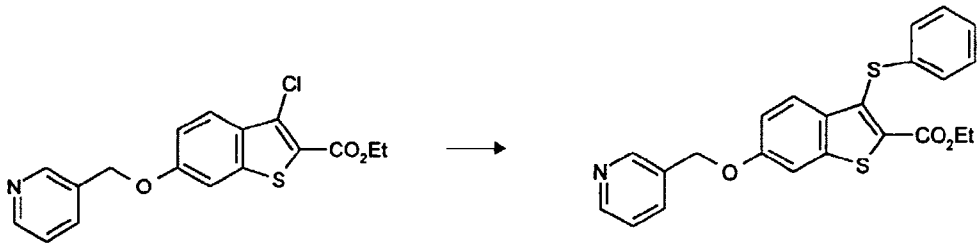
[0095] Trifluoroacetic acid (50ml) was added to a stirred mixture of ethyl 6-(benzyloxy)-3-(phenylsulfinyl)benzo[*b*]thiophene-2-carboxylate (Example 31, 4.9g, 11.2mmol) and methyl phenyl sulfide (5.2ml, 45mmol) at ambient temperature under a nitrogen atmosphere. After 20 hours the solvents were removed under reduced pressure, and the residue was azeotroped using toluene. The residue was flash chromatographed on silica gel using 2% ethanol in dichloromethane as eluant. The isolated product was crystallised from diisopropyl ether to give the title compound as a colourless

solid (3.05g).
m.p. 185-187°C
LRMS (Thermospray): 347.4 (MH^+)
^{1}H NMR (300MHz, DMSO-d_6): δ = 1.33 (t, 3H), 4.40 (q, 2H), 6.92 (dd, 1H), 7.36 (s, 1H), 7.42-7.58 (m, 3H), 7.79 (d, 2H), 8.41 (d, 1H), 10.25 (brs, 1H).
Analysis: Found: C, 58.76; H, 4.03.
$C_{17}H_{14}O_4S_2$ Requires: C, 58.94; H, 4.07.

Example 1

Ethyl 3-(phenylsulfanyl)-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0096]

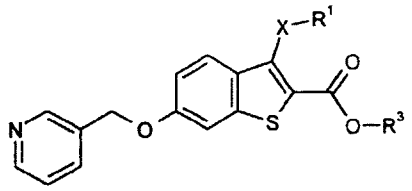


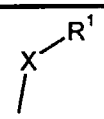
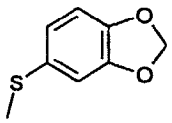
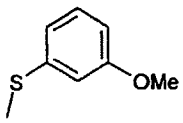
[0097] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU - 1.46ml, 9.5mmol) was added to a mixture of ethyl 3-chloro-6-(3-pyridylmethoxy)benzo[b]thiophene-2-carboxylate (Preparation 4, 3.0g 8.6mmol) and thiophenol (1.76ml, 17.2mmol) in dimethylformamide (15ml) under a nitrogen atmosphere. The solution was heated to 60°C for 5 hours and then partitioned between diethyl ether and water. The organics were separated and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using diethyl ether, and then ethyl acetate, as eluant. The isolated product was crystallised from diethyl ether and hexane to give the title compound as a colourless solid (2.85g).
m.p. 94-95°C
LRMS (Thermospray): 422.2 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.33 (t, 3H), 4.36 (q, 2H), 5.13 (s, 2H), 7.00 (dd, 1H), 7.06-7.24 (m, 5H), 7.30-7.37 (m, 2H), 7.70 (d, 1H), 7.78 (d, 1H), 8.60 (d, 1H), 8.70 (s, 1H).
Analysis: Found: C, 65.23; H, 4.50; N, 3.28.
$C_{23}H_{19}NO_3S_2$ Requires: C, 65.53; H, 4.54; N, 3.32.

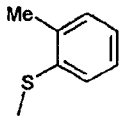
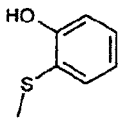
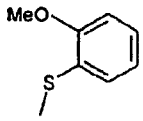
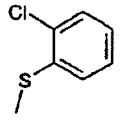
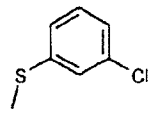
Examples 2-15

[0098] These were prepared by the method of Example 1, using the appropriate substituted thiophenol and benzo [*b*]thiophene starting materials as described in Preparations 3, 4, 5 or 7.
[0099] Their physical data are shown in Table 1 and Table 2.

Table 1



Example N°		R^3	Physical Data
2		Me	**m.p.** 126-128°C **LRMS** (Thermospray): 452.3 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 3.84 (s, 3H), 5.14 (s, 2H), 5.90 (s, 2H), 6.66 (d, 1H), 6.74 (s, 1H), 6.86 (d, 1H), 7.02 (dd, 1H), 7.34 (m, 2H), 7.77 (m, 2H), 8.60 (d, 1H), 8.71 (s, 1H). **Analysis:** Found: C, 61.18; H, 3.80, N, 3.10. $C_{23}H_{17}NO_5S_2$ Requires: C, 60.96; H, 4.82; N, 3.03.
3		Et	**m.p.** 85-86°C (from diethyl ether/hexane) **LRMS** (APCI): 451.9 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.36 (t, 3H), 3.70 (s, 3H), 4.38 (q, 2H), 5.13 (s, 2H), 6.65 (dd, 1H), 6.70-6.75 (m, 2H), 7.02 (dd, 1H), 7.10 (t, 1H), 7.35 (m, 2H), 7.70 (d, 1H), 7.78 (d, 1H), 8.60 (d, 1H), 8.71 (s, 1H). **Analysis:** Found: C, 63.57; H, 4.68, N, 3.10.

			$C_{24}H_{21}NO_4S_2$ Requires: C, 63.83; H, 4.69; N, 3.10.
4		Et	**LRMS** (Thermospray): 435.8 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.33 (t, 3H), 2.47 (s, 3H), 4.38 (q, 2H), 5.14 (s, 2H), 6.80 (d, 1H), 6.90-7.10 (m, 3H), 7.17 (d, 1H), 7.33-7.38 (m, 2H), 7.59 (d, 1H), 7.78 (d, 1H), 8.61 (d, 1H), 8.70 (s, 1H). **Analysis:** Found: C, 65.95; H, 4.85, N, 3.21. $C_{24}H_{21}NO_3S_2$ Requires: C, 66.18; H, 4.86; N, 3.22.
5		Et	**m.p.** 172-174°C (from ethyl acetate) **LRMS** (Thermospray): 438.2 (MH^-) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 1.24 (t, 3H), 4.30 (q, 2H), 5.20 (s, 2H), 6.57-6.67 (m, 2H), 6.80 (d, 1H), 6.98 (t, 1H), 7.06 (d, 1H), 7.40 (dd, 1H), 7.55 (d, 1H), 7.75 (s, 1H), 7.87 (d, 1H), 8.54 (d, 1H), 8.67 (s, 1H), 10.02 (s, 1H). **Analysis:** Found: C, 63.35; H, 4.29, N, 3.13. $C_{23}H_{19}NO_4S_2$ Requires: C, 63.14; H, 4.38; N, 3.20.
6		Et	**LRMS** (Thermospray): 452.1 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.33 (t, 3H), 3.89 (s, 3H), 4.36 (q, 2H), 5.13 (s, 2H), 6.70 (m, 2H), 6.85 (d, 1H), 7.01 (dd, 1H), 7.10 (m, 1H), 7.30-7.38 (m, 2H), 7.70-7.80 (m, 2H), 8.60 (d, 1H), 8.72 (s, 1H). $C_{24}H_{21}NO_4S_2$
7		Et	**m.p.** 137-139°C **LRMS** (Thermospray): 456.6 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ =.1.30 (t, 3H), 4.36 (q, 2H), 5.18 (s, 2H), 6.64 (d, 1H), 6.90-7.10 (m, 3H), 7.30-7.40 (m, 3H), 7.75 (d, 1H), 7.80 (d, 1H) 8.62 (br, 1H), 8.73 (br, 1H). $C_{23}H_{18}ClNO_3S_2$
8		Et	**m.p.** 114-116°C **LRMS** (Thermospray): 456.6 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ =.1.34 (t, 3H), 4.38 (q, 2H), 5.18 (s, 2H), 6.98-7.13 (m, 5H), 7.30-7.40 (m, 2H), 7.75 (d, 1H), 7.80 (d, 1H) 8.62 (br.d, 1H), 8.72 (br.s, 1H). $C_{23}H_{18}ClNO_3S_2$
			m.p. 108-110°C

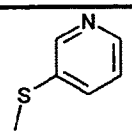
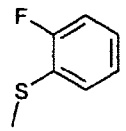
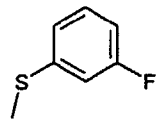
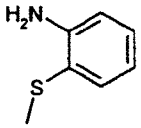
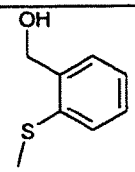
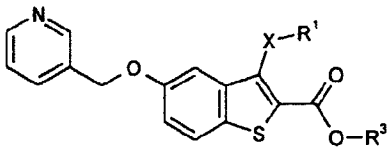
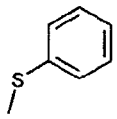
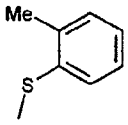
9		Et	**LRMS** (Thermospray): 423.0 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.36 (t, 3H), 4.38 (d, 2H), 5.18 (s, 2H), 7.03-7.15 (m, 2H), 7.30-7.50 (m, 3H), 7.75-7.81 (m, 2H), 8.38 (d, 1H), 8.43 (s, 1H), 8.62 (d, 1H), 8.72 (s, 1H). $C_{22}H_{18}N_2O_3S_2$
10		Et	**m.p.** 85°C (from diisopropyl ether) **LRMS** (Thermospray): 440.4 (MH^-) **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.30 (t, 3H), 4.33 (q, 2H), 5.13 (s, 2H), 6.85-7.15 (m, 5H), 7.30 (m, 2H), 7.75 (m, 2H), 8.58 (d, 1H), 8.67 (s, 1H). $C_{23}H_{18}FNO_3S_2$
11		Et	**m.p.** 110°C (from diisopropyl ether) **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.30 (t, 3H), 4.35 (q, 2H), 5.12 (s, 2H), 6.78 (m, 2H), 6.90 (d, 1H), 7.03 (d, 1H), 7.14 (m, 1H), 7.32 (m, 2H), 7.70-7.80 (m, 2H), 8.58 (d, 1H), 8.69 (s, 1H). $C_{23}H_{18}FNO_3S_2$
12		Et	**m.p.** 103-105°C (from diethyl ether/hexane) **LRMS** (Thermospray): 437.3 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 1.32 (t, 3H), 4.35 (q, 2H), 5.20 (s, 2H), 5.44 (s, 2H), 6.48 (t, 1H), 6.68 (d, 1H), 6.98-7.07 (m, 2H), 7.20 (d, 1H), 7.40 (dd, 1H), 7.61 (d, 1H), 7.70 (s, 1H), 7.85 (d, 1H), 8.53 (d, 1H), 8.66 (s, 1H). $C_{23}H_{20}N_2O_3S_2$
13		Et	**LRMS** (Thermospray): 452.0 (MH^+). **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.33 (t, 3H), 2.73 (brs, 1H), 4.35 (q, 2H), 4.90 (s, 2H), 5.18 (s, 2H), 6.89 (d, 1H), 7.03-7.10 (m, 2H), 7.19 (t, 1H), 7.32-7.40 (m, 2H), 7.43 (d, 1H), 7.77-7.83 (m, 2H), 8.63 (2, 1H), 8.73 (s, 1H). $C_{24}H_{21}NO_4S_2$

Table 2

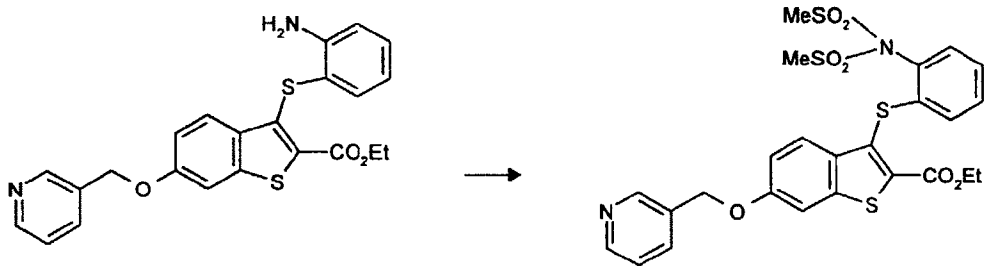


Example N°		R^3	Physical Data
14		Me	**LRMS** (APCI): 408.2 (MH^+) **^{1}H NMR** (400MHz, DMSO-d_6): δ = 3.75 (s, 3H), 5.02 (s, 2H), 7.16-7.33 (m, 7H), 7.38 (m, 1H), 7.77 (d, 1H), 8.02 (d, 1H), 8.51 (d, 1H), 8.60 (s, 1H). $C_{22}H_{17}NO_3S_2$
15		Et	**m.p.** 95°C (from diethyl ether) **LRMS** (Thermospray): 436.2 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.35 (t, 3H), 2.46 (s, 3H), 4.38 (q, 2H), 4.84 (s, 2H), 6.88 (d, 1H), 6.98 (t, 1H), 7.09 (t, 1H), 7.12-7.20 (m, 3H), 7.28 (m, 1H), 7.67 (d, 1H), 7.74 (d, 1H), 8.60 (m, 2H). **Analysis:** Found: C, 66.07; H, 4.81, N, 3.15. $C_{24}H_{21}NO_3S_2$ Requires: C, 66.18; H, 4.86; N, 3.22.

Example 16

Ethyl 3-[2-(N,N-dimethylsulfonylamino)phenyl]sulfanyl-6-(3-pyridylmethoxy) benzo[*b*]thiophene-2-carboxylate

[0100]



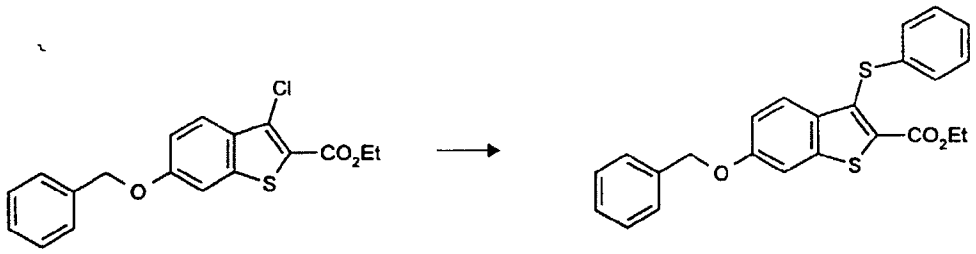
[0101] Methanesulfonyl chloride (0.86ml, 1.1mmol) was added to a stirred solution of ethyl 3-[(2-aminophenyl)sulfanyl]-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate (Example 12 220mg, 0.5mmol) and N,N-diisopropylethylamine (0.2ml, 1.1mmol) in dichloromethane (3ml). The mixture was left at ambient temperature for 20 hours and then diluted with dichloromethane and washed with water. The organics were dried (magnesium sulfate), and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using diethyl ether, and then ethyl acetate, as eluant. The title product was crystallised from diethyl ether to give a colourless solid (232mg).
m.p. 165-167°C

LRMS (Thermospray): 593.5 (MH^+)
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.33 (t, 3H), 3.63 (s, 6H), 4.36 (q, 2H), 5.14 (s, 2H), 6.66 (d, 1H), 7.03 (dd, 1H), 7.10-7.20 (m, 2H), 7.30-7.39 (m, 3H), 7.70-7.80 (m, 2H), 8.60 (d, 1H), 8.70 (s, 1H).
$C_{25}H_{24}N_2O_7S_4$

Example 17

Ethyl 6-(benzyloxy)-3-(phenylsulfanyl)benzo[*b*]thiophene-2-carboxylate

[0102]

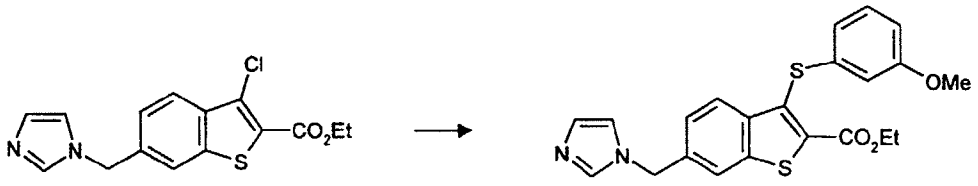


[0103] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU - 0.39ml, 2.5mmol) was added to a mixture of ethyl 6-(benzyloxy)-3-chlorobenzo[*b*]thiophene-2-carboxylate (Preparation 8, 800mg, 2.3mmol) and thiophenol (0.47ml, 4.6mmol) in dimethylformamide (4ml) under a nitrogen atmosphere. The solution was heated to 60°C for 6 hours and then partitioned between diethyl ether and water. The organics were separated and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using a mixture of 20% dichloromethane and 80% hexane, then 50% dichloromethane and 50% hexane as eluant. The isolated product was crystallised from diisopropyl ether and hexane to give the title compound as a colourless solid (810mg).
m.p. 96-97°C
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.36 (t, 3H), 4.35 (q, 2H), 5.13 (s, 2H), 7.02 (dd, 1H), 7.10-7.24 (m, 5H), 7.30-7.50 (m, 6H), 7.70 (d, 1H).
Analysis: Found: C, 68.16; H, 4.74.
$C_{24}H_{20}O_3S_2$ Requires: C, 68.54; H, 4.79.

Example 18

Ethyl 6-(1*H*-1-imidazolylmethyl)-3-[(3-methoxyphenyl)sulfanyl]benzo[*b*]thiophene-2-carboxylate

[0104]

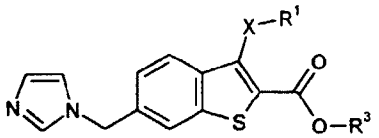


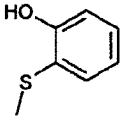
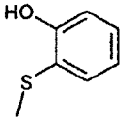
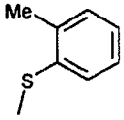
[0105] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU - 0.26ml, 1.7mmol) was added to a mixture of ethyl 3-chloro-6-(1*H*-1-imidazolylmethyl)benzo[*b*]thiophene-2-carboxylate (Preparation 11, 500mg, 1.6mmol) and 3-methoxybenzenethiol (0.29ml, 2.3mmol) in dimethylformamide (2ml) under a nitrogen atmosphere. The solution was heated to 60°C for 5 hours and then partitioned between ethyl acetate and water. The organics were separated and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using 5% methanol in dichloromethane as eluant to give the title compound as a gum (615mg).
LRMS (Thermospray): 424.7 (MH^+)
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.38 (t, 3H), 3.70 (s, 3H), 4.40 (q, 2H), 5.27 (s, 2H), 6.65-6.75 (m, 3H), 6.94 (s, 1H), 7.08-7.19 (m, 3H), 7.60 (s, 1H), 7.72 (s, 1H), 7.80 (d, 1H).
$C_{22}H_{20}N_2O_3S_2$

Examples 19-21

[0106] These were prepared by the method of Example 18, using the appropriate substituted thiophenol and benzo [*b*]thiophene starting materials.
Their physical data are shown in Table 3.

Table 3

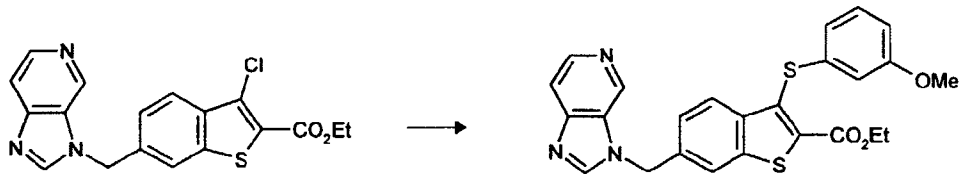


Example N°		R^3	Physical Data
19		Et	**LRMS** (Thermospray): 411.3 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.48 (q, 2H), 5.22 (s, 2H), 6.80 (t, 1H), 6.87-6.95 (m, 2H), 7.10 (s, 1H), 7.16-7.28 (m, 2H), 7.50 (s, 1H), 7.55 (s, 1H), 7.70 (d, 1H), 8.22 (d, 1H), 8.60 (brs, 1H). $C_{21}H_{18}N_2O_3S_2$
20		Me	**m.p.** 188-190°C (from methanol) **LRMS** (Thermospray): 397.2 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.82 (s, 3H), 5.30 (s, 2H), 6.60 (t, 1H), 6.67 (d, 1H), 6.80 (d, 1H), 6.90 (s, 1H), 7.00 (t, 1H), 7.20 (s, 1H), 7.25 (d, 1H), 7.62 (d, 1H), 7.77 (s, 1H), 7.92 (s, 1H), 10.03 (s, 1H). $C_{20}H_{16}N_2O_3S_2$
21		Et	**m.p.** 88-89°C (from diethyl ether/hexane) **LRMS** (Thermospray): 409.2 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.34 (t, 3H), 2.46 (s, 3H), 4.36 (q, 2H), 5.22 (s, 2H), 6.80 (d, 1H), 6.88-6.98 (m, 2H), 7.00-7.20 (m, 4H), 7.55 (s, 1H), 7.59 (s, 1H), 7.63 (d, 1H). **Analysis:** Found: C, 64.34; H, 4.91, N, 6.74. $C_{22}H_{20}N_2O_2S_2$ Requires: C, 64.68; H, 4.93; N, 6.86.

Example 22

Ethyl 6-(3*H*-imidazo[4,5-*c*]pyridin-3-ylmethyl)-3-[(3-methoxyphenyl)sulfanyl] benzo[*b*]thiophene-2-carboxylate

[0107]



[0108] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU - 0.07ml, 0.48mmol) was added to a mixture of ethyl 3-(chloro)-6-(3*H*-imidazo[4,5-*c*]pyridin-3-ylmethyl)benzo[*b*]thiophene-2-carboxylate (Preparation 12, 150mg, 0.4mmol) and 3-methoxybenzenethiol (0.07ml, 0.6mmol) in a mixture of dimethylformamide (1ml) and tetrahydrofuran (1ml) under a nitrogen atmosphere. The solution was heated to 60°C for 6 hours and then partitioned between ethyl acetate and water. The organics were separated and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residue was triturated with diethyl ether and hexane mixture to give the title compound as a colourless solid (155mg).

LRMS (Thermospray): 476.3 (MH^+)

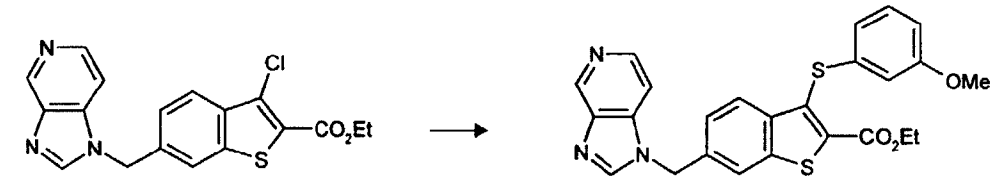
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.38 (t, 3H), 3.68 (s, 3H), 4.39 (q, 2H), 5.55 (s, 2H), 6.63-6.75 (m, 3H), 7.10 (t, 1H), 7.19 (d, 1H), 7.65 (s, 1H), 7.74 (d, 1H), 7.81 (d, 1H), 8.08 (s, 1H), 8.48 (d, 1H), 8.75 (s, 1H).

$C_{25}H_{21}N_3O_3S_2$

Example 23

Ethyl 6-(1*H*-imidazo [4,5-*c*]pyridin-1-ylmethyl)-3-[(3-methoxyphenyl)sulfanyl] benzo[*b*]thiophene-2-carboxylate

[0109]



[0110] This example was prepared from the intermediate of Preparation 13, using the same method as described for Example 22, to give the title compound as a colourless solid.

LRMS (Thermospray): 476.3 (MH^+)

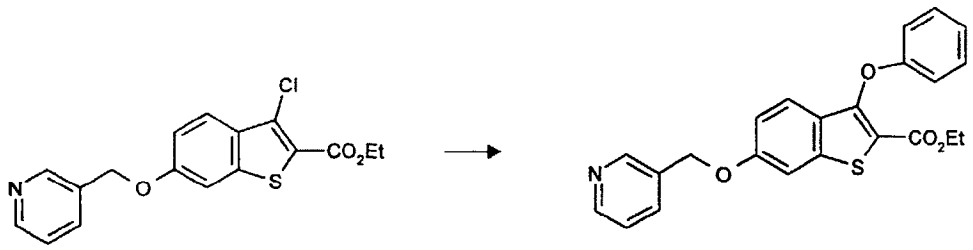
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.37 (t, 3H), 3.68 (s, 3H), 4.38 (q, 2H), 5.49 (s, 2H), 6.63-6.75 (m, 3H), 7.10 (t, 1H), 7.15 (d, 1H), 7.23 (d, 1H), 7.60 (s, 1H), 7.80 (d, 1H), 8.01 (s, 1H), 8.42 (d, 1H), 9.18 (s, 1H).

$C_{25}H_{21}N_3O_3S_2$

Example 24

Ethyl 3-(phenoxy)-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0111]



[0112] Phenol (108mg, 1.15mmol) was added to a stirred suspension of sodium hydride (46mg of 60% dispersion in mineral oil, 1.15 mmol) in anhydrous dimethylformamide (1ml), under a nitrogen atmosphere. Ethyl 3-chloro-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate (Preparation 4, 200mg, 0.58mmol) was added to the mixture after 30 minutes, and the mixture was then heated to 75°C for 48 hours. The reaction was partitioned between ethyl acetate and water. The organics were separated and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using diethyl ether as eluant. The isolated product was crystallised from hexane to give the title compound as a colourless solid (40mg).

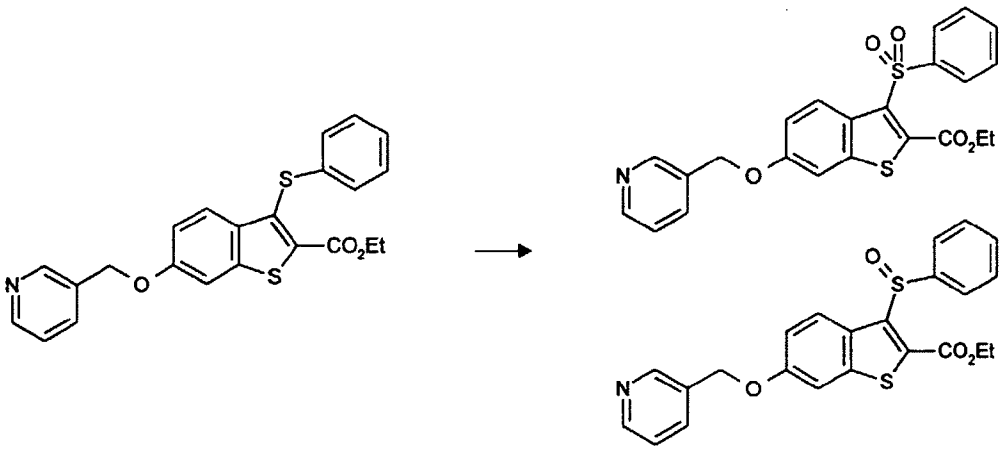
LRMS (Thermospray): 406.5 (MH^+)

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.18 (t, 3H), 4.23 (q, 2H), 5.17 (s, 2H), 6.93 (d, 2H), 6.98-7.08 (m, 2H), 7.22-7.40 (m, 4H), 7.57 (d, 1H), 7.80 (d, 1H), 8.62 (d, 1H), 8.71 (s, 1H).

$C_{23}H_{19}NO_4S$.

Example 25 & 26

[0113]



Example 25

Ethyl 3-(phenylsulfonyl)-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0114] Hydrogen peroxide in water (0.42ml of 30%w/v, 3.75mmol) was added to a solution of ethyl 3-(phenylsulfanyl)-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate (Example 1, 633mg, 1.5mmol) in acetic acid (4.5ml). The mixture was heated to 100°C for 90 minutes. The solvents were removed by evaporation under reduced pressure, and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was separated, dried (magnesium sulfate) and concentrated under vacuo, and the residue flash chromatographed on silica gel using 1% methanol in dichloromethane as eluant. The less polar product was isolated and crystallised from dichlo-

romethane and diethyl ether to give the title compound as a colourless solid (230mg).
m.p. 120-122°C
LRMS (Thermospray): 454.1 (MH^+)
Analysis: Found: C, 60.93; H, 4.43; N, 2.98.
$C_{23}H_{19}NO_5S_2$ Requires: C, 60.91; H, 4.22; N, 3.09.
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.41 (t, 3H), 4.44 (q, 2H), 5.15 (s, 2H), 7.22 (dd, 1H), 7.27-7.38 (m, 2H), 7.48-7.60 (m, 3H), 7.78 (d, 1H), 8.18 (d, 2H), 8.49 (d, 1H), 8.60 (d, 1H), 8.70 (s, 1H).

Example 26

Ethyl 3-(phenylsulfinyl)-6-(3-pyridylmethoxy)benzo [*b*]thiophene-2-carboxylate

[0115] The more polar product from the previous reaction was isolated by continuation of the flash chromatography to give this title compound which was crystallised from dichloromethane and diethyl ether to give a colourless solid (220mg).
m.p. 118-120°C
LRMS (Thermospray): 438.1 (MH^+)
Analysis: Found: C, 62.94; H, 4.28; N, 3.52.
$C_{23}H_{19}NO_4S_2$ Requires: C, 63.14; H, 4.38; N, 3.20.
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.43 (q, 2H), 5.11 (s, 2H), 7.07 (dd, 1H), 7.24-7.50 (m, 5H), 7.77 (d, 1H), 7.89 (d, 2H), 8.60 (d, 1H), 8.67 (s, 1H), 8.70 (d, 1H).

Examples 27-29

[0116] These were prepared by the method of Example 26, using the appropriately substituted 3-arylsulfanyl-benzo [*b*]thiophene starting materials from Table 1, except that only 1.2 equivalents of hydrogen peroxide were used, to maximise the yield of the sulfinyl analogue. Their physical data are shown in Table 4.

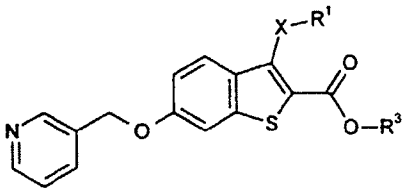
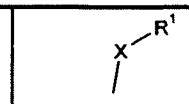
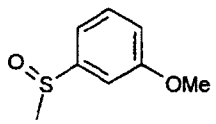
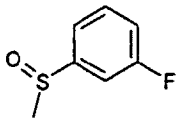
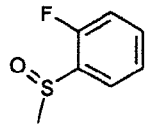


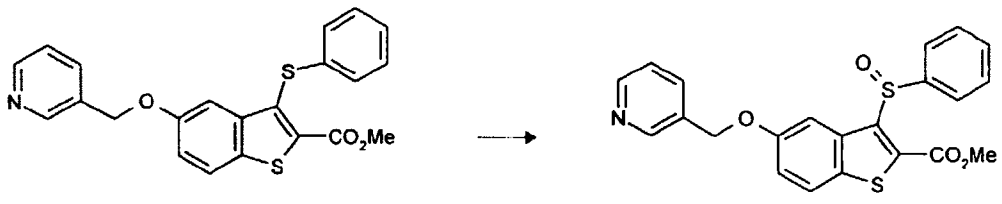
Table 4

Example N°		R^3	Physical Data
27		Et	**m.p.** 132-134°C (from diethyl ether) **LRMS** (Thermospray): 468.5 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.42 (t, 3H), 3.82 (s, 3H), 4.45 (q, 2H), 5.13 (s, 2H), 6.92 (dd, 1H), 7.07 (dd, 1H), 7.28-7.43 (m, 4H), 7.50 (s, 1H), 7.78 (d, 1H), 8.60 (d, 1H), 8.68 (s, 1H), 8.70 (d, 1H). **Analysis**: Found: C, 61.26; H, 4.47; N, 2.94. $C_{24}H_{21}NO_5S_2$ Requires: C, 61.66; H, 4.53; N, 3.00.
28		Et	**m.p.** 135-137°C (from diisopropyl ether) **LRMS** (Thermospray): 455.7 (MH^+) **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.40 (t, 3H), 4.42 (m, 2H), 5.09 (s, 2H), 7.05 (m, 2H), 7.20-7.40 (m, 3H), 7.57-7.75 (m, 3H), 8.58-8.68 (m, 3H). $C_{23}H_{18}FNO_4S_2$.
29		Et	**m.p.** 150-151°C (from diisopropyl ether) **LRMS** (Thermospray): 456.1 (MH^+) **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.38 (t, 3H), 4.40 (m, 2H), 5.12 (s, 2H), 6.96-7.05 (m, 2H), 7.26-7.42 (m, 4H), 7.73 (d, 1H), 8.00 (dd, 1H), 8.52-8.60 (m, 2H), 8.66 (s, 1H). $C_{23}H_{18}FNO_4S_2$.

Example 30

Methyl 3-(phenylsulfinyl)-5-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0117]



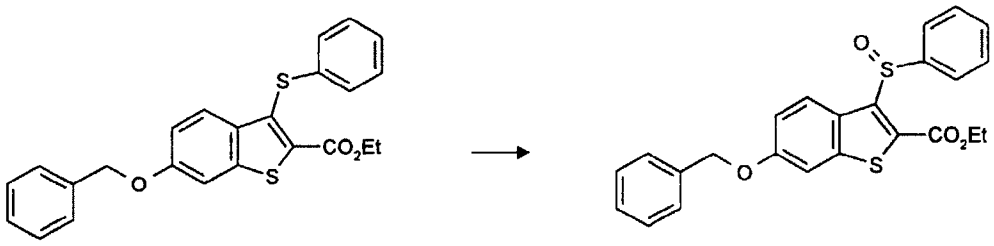
[0118] This example was prepared using the same method as described for Example 26, using the 3-(phenylsulfanyl) benzo[*b*]thiophene derivative from Example 14.
LRMS (APCI): 424.0 (MH^+)

^{1}H NMR (400MHz, DMSO-d_6): δ = 3.96 (s, 3H), [5.10 (d, 1H) / 5.09 (d, 1H) non-equivalent $OC\underline{H}_2Py^3$], 7.31 (d, 1H), 7.42 (dd, 1H), 7.45-7.55 (m, 3H), 7.77 (d, 2H), 7.86 (d, 1H), 8.03 (d, 1H), 8.17 (s, 1H), 8.57 (d, 1H), 8.68 (s, 1H).
$C_{22}H_{17}NO_4S_2$

Example 31

Ethyl 6-(benzyloxy)-3-(phenylsulfinyl)benzo[*b*]thiophene-2-carboxylate

[0119]

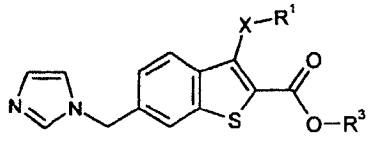


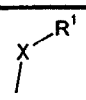
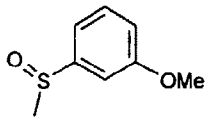
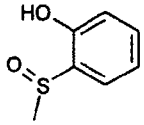
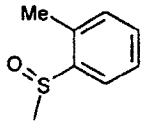
[0120] Hydrogen peroxide in water (0.15ml of 30%w/v, 1.3mmol) was added to a solution of ethyl 6-(benzyloxy)-3-(phenylsulfanyl)benzo[*b*]thiophene-2-carboxylate (Example 17 - 500mg, 1.2mmol) in acetic acid (5ml) and tetrahydrofuran (5ml). The mixture was heated to 100°C for 3 hours. The solvents were removed by evaporation under reduced pressure, and the residue was partitioned between diethyl ether and aqueous sodium bicarbonate solution. The organic layer was separated, dried (magnesium sulfate) and concentrated under vacuo, and the residue was crystallised from dichloromethane and diisopropyl ether to give the title compound as a colourless solid (455mg).
m.p. 141-142°C
Analysis: Found: C, 65.74; H, 4.54.
$C_{24}H_{20}O_4S_2$ Requires: C, 66.03; H, 4.62.
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 4.47 (q, 2H), 5.10 (s, 2H), 7.08 (dd, 1H), 7.27-7.53 (m, 9H), 7.90 (d, 2H), 8.70 (d, 1H).

Examples 32-34

[0121] These were prepared by the method of Example 31, using the appropriate 3-(phenylsufanyl)benzo[*b*]thiophene derivatives from Examples 18, 19 and 21. Their physical data are shown in Table 5.

Table 5

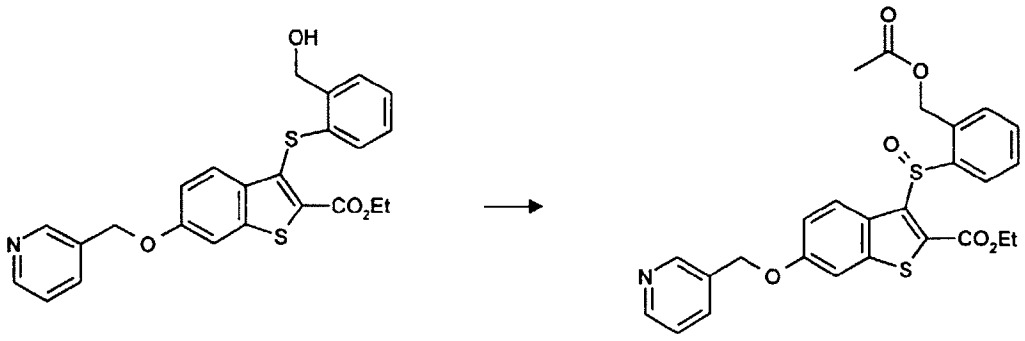


Example N°		R^3	Physical Data
32		Et	**m.p.** 149-151°C (from diethyl ether) **LRMS** (Thermospray): 441.3 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 3.80 (s, 3H), 4.47 (q, 2H), 5.21 (s, 2H), 6.85-6.95 (m, 2H), 7.10 (s, 1H), 7.19 (d, 1H), 7.30-7.40 (m, 2H), 7.45-7.53 (m, 2H), 7.58 (s, 1H), 8.74 (d, 1H). $C_{22}H_{20}N_2O_4S_2$
33		Et	**m.p.** 195-196°C (from ethyl acetate) **HRMS** (+ve ion electrospray): 427.1 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 1.34 (t, 3H), 4.39 (q, 2H), 5.26 (s, 2H), 6.73 (d, 1H), 6.89 (s, 1H), 7.01 (t, 1H), 7.17 (s, 1H), 7.20-7.30 (m, 2H), 7.73 (s, 1H), 7.81 (d, 1H), 7.90 (s, 1H), 8.38 (d, 1H), 10.42 (s, 1H). **Analysis:** Found: C, 58.83; H, 4.24; N, 6.44. $C_{21}H_{18}N_2O_4S_2$ Requires: C, 59.13; H, 4.25; N, 6.57.
34		Et	**m.p.** 140-142°C (from diethyl ether) **LRMS** (Thermospray): 425.3 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.39 (t, 3H), 2.50 (s, 3H), 4.38 (m, 2H), 5.23 (s, 2H), 6.92 (s, 1H), 7.12 (s, 1H), 7.17-7.37 (m, 4H), 7.53 (s, 1H), 7.58 (s, 1H), 7.85 (d, 1H), 8.70 (d, 1H). $C_{22}H_{20}N_2O_3S_2$

Example 35

Ethyl 3-(2-[(methylcarbonyloxy)methyl]phenylsulfinyl)-6-(3-pyridylmethoxy) benzo[*b*]thiophene-2-carboxylate

[0122]

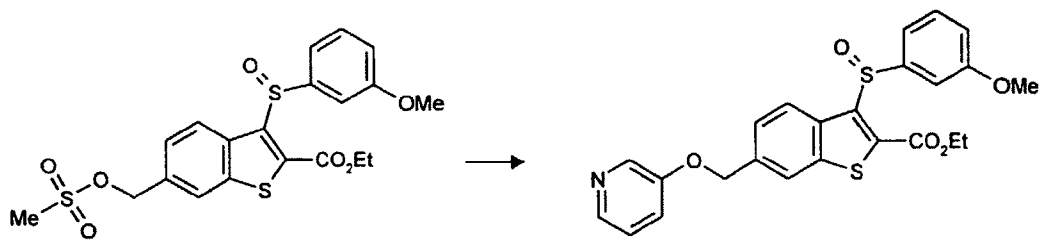


[0123] Hydrogen peroxide in water (0.23ml of 30% w/v, 2.05mmol) was added to a mixture of ethyl 3-[2-(hydroxymethyl)phenylsulfanyl]-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate (Example 13, 770mg, 1.71mmol) in acetic acid (5ml), and 2M aqueous hydrochloric acid (0.8ml). The mixture was heated to 100°C for 3 hours, cooled, and the solvents removed under reduced pressure. The residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, and the organic layer was separated, dried (magnesium sulfate) and concentrated under vacuo. The residue was flash chromatographed on silica gel using a mixture of 75% ethyl acetate and 25% hexane as eluant, to give the title compound as a colourless solid (500mg).
LRMS (Thermospray): 510.2 (MH^+)
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.38 (t, 3H), 2.04 (s, 3H), 4.38 (m, 2H), 5.15 (s, 2H), [5.27 (d, 1H) & 5.60 (d, 1H) non-equivalent CH_2OAc], 7.10 (d, 1H), 7.35 (m, 2H), 7.45 (m, 3H), 7.79 (d, 1H), 7.97 (dd, 1H), 8.61 (d, 1H), 8.70 (s, 1H), 8.78 (d, 1H).
$C_{26}H_{23}NO_6S_2$

Example 36

Ethyl 3-[(3-methoxyphenyl)sulfinyl]-6-[(3-pyridyloxy)methyl]benzo[*b*]thiophene-2-carboxylate

[0124]



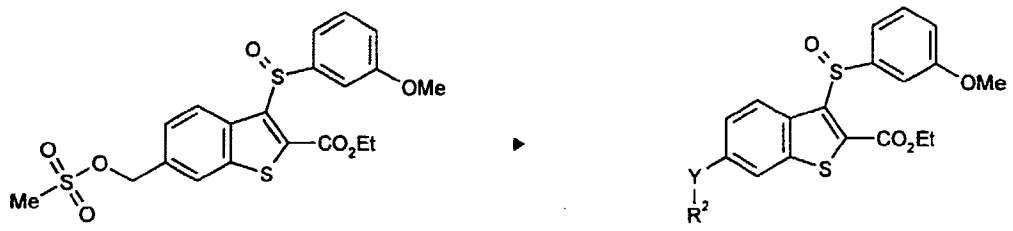
[0125] 3-Hydroxypyridine (57mg, 0.6mmol) was added to a stirred suspension of sodium hydride (24mg of 60% dispersion in mineral oil, 0.6mmol) in anhydrous dimethylformamide (2ml), under a nitrogen atmosphere. After 30 minutes, ethyl 3-[(3-methoxyphenyl)sulfinyl]-6-[(methylsulfonyloxy)methyl]benzo[*b*]thiophene-2-carboxylate (Preparation 18, 234mg, 0.5mmol) was added to the mixture, and the mixture was stirred for 3 hours. The reaction was partitioned between ethyl acetate and water. The organics were separated and washed with water, dried (magnesium sulfate) and evaporated under reduced pressure. The residue was flash chromatographed on silica gel using 2% ethanol in dichloromethane as eluant. The semi-pure product was re-chromatographed on silica gel using ethyl acetate, and then crystallised from diethyl ether, to give the title compound as a colourless solid (110mg).
m.p. 113-115°C (from diethyl ether)

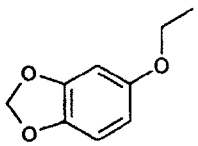
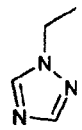
LRMS (Thermospray): 468.3 (MH^+) for $C_{24}H_{21}NO_5S_2$
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.47 (t, 3H), 3.81 (s, 3H), 4.50 (q, 2H), 5.20 (s, 2H), 6.92 (d, 1H), 7.17-7.27 (m, 2H), 7.33 (t, 1H), 7.39-7.47 (m, 2H), 7.51(s, 1H), 7.90 (s, 1H), 8.24 (d, 1H), 8.40 (s, 1H), 8.80 (d, 1H).

Examples 37-38

[0126] These were prepared by the method of Example 36, using 3,4-(methylenedioxy)phenol for Example 37, and 1,2,4-triazole for Example 38, in place of 3-hydroxypyridine. Their physical data are shown in Table 6.

Table 6

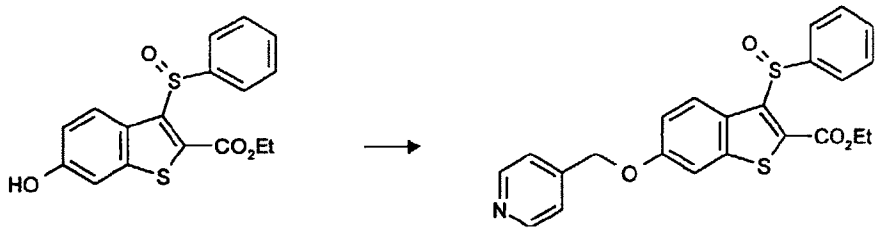


Example N°	Y / R²	Physical Data
37		**m.p.** 133-135°C (from diethyl ether and hexane) **LRMS** (APCI): 511.1 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.44 (t, 3H), 3.82 (s, 3H), 4.49 (q, 2H), 5.07 (s, 2H), 5,92 (s, 2H), 6.38 (dd, 1H), 6.55 (s, 1H), 6.69 (d, 1H), 6.92 (dd, 1H), 7.30-7.45 (m, 3H), 7.52 (s, 1H), 7.90 (s, 1H), 8.75 (d, 1H).
		Analysis: Found: C, 61.67; H, 4.74; N, 0.00. $C_{26}H_{22}O_7S_2$ Requires: C, 61.16; H, 4.34; N, 0.00.
38		**m.p.** 148-149°C (from diethyl ether) **LRMS** (Thermospray): 442.0 (MH^+) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 3.80 (s, 3H), 4.50 (q, 2H), 5.42 (s, 2H), 6.92 (d, 1H), 7.23-7.40 (m, 3H), 7.47 (s, 1H), 7.68 (s, 1H), 7.98 (s, 1H), 8.10 (s, 1H), 8.77 (d, 1H). **Analysis:** Found: C, 56.66; H, 4.24; N, 9.20. $C_{21}H_{19}N_3O_4S_2$ Requires: C, 57.12; H, 4.34; N, 9.52.

Example 39

Ethyl 3-[(3-methoxyphenyl)sulfinyl]-6-(4-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate

[0127]



[0128] Potassium carbonate (240mg, 1.73mmol) was added to a solution of ethyl 6-hydroxy-3-(phenylsulfinyl)benzo [*b*]thiophene-2-carboxylate (Preparation 19, 200mg, 0.58mmol) in anhydrous dimethylformamide (3ml) at ambient temperature under a nitrogen atmosphere. After 15 minutes 4-(chloromethyl)pyridine hydrochloride (104mg, 0.64mmol) was added, and stirring continued for 24 hours. The mixture was partitioned between ethyl acetate and water, and the organic layer was separated and washed twice with water, dried (magnesium sulfate), and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate as eluant, and crystallised from diisopropyl ether to give the title compound as a colourless solid (198mg).

m.p. 153-155°C

LRMS (Thermospray): 438.2 (MH^+)

Analysis: Found: C, 62.96; H, 4.36; N, 3.10.

$C_{23}H_{19}NO_4S_2$ Requires: C, 63.14; H, 4.38; N, 3.20.

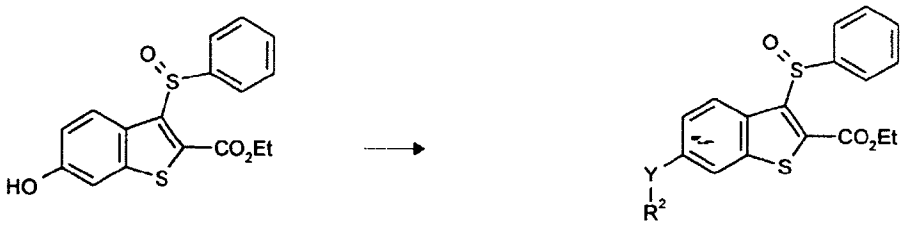
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 4.46 (q, 2H), 5.15 (s, 2H), 7.07 (dd, 1H), 7.26 (s, 1H), 7.33 (d, 2H), 7.40-7.50 (m, 3H), 7.90 (d, 2H), 8.62 (d, 2H), 8.73 (d, 1H).

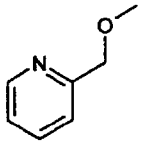
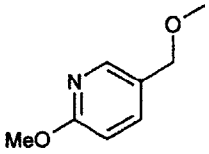
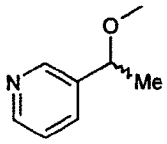
Examples 40-51

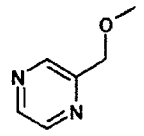
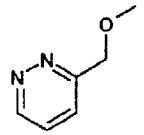
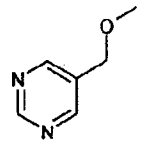
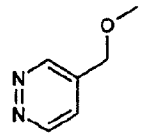
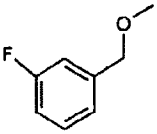
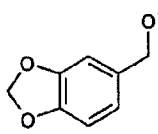
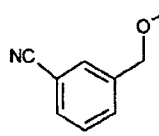
[0129] These were prepared following the method of Example 39, by reacting the appropriate alkylating agents such as R^2-CH_2-Cl, and R^2-$CH(CH_3)$-Cl, with the intermediate from Preparation 19. These alkylating agents are either commercially available or prepared as described in the chemical literature.

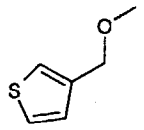
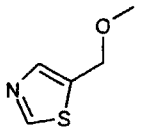
Their physical data are shown in Table 7.

Table 7



Example N°		Physical Data
40		**LRMS** (Thermospray): 437.9 (MH^+) **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.43 (q, 2H), 5.22 (s, 2H), 7.09 (d, 1H), 7.22 (dd, 1H), 7.30 (s, 1H), 7.37-7.50 (m, 4H), 7.70 (dd, 1H), 7.90 (d, 2H), 8.59 (d, 1H), 8.70 (d, 1H). $C_{23}H_{19}NO_4S_2$.
41		**m.p.** 123-125°C (from diisopropyl ether) **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.44 (t, 3H), 3.95 (s, 3H), 4.45 (q, 2H), 5.02 (s, 2H), 6.78 (d, 1H), 7.04 (dd, 1H), 7.29 (s, 1H), 7.40-7.49 (m, 3H), 7.63 (dd, 1H), 7.90 (d, 2H), 8.20 (s, 1H), 8.70 (d, 1H). **Analysis:** Found: C, 61.38; H, 4.52; N, 3.01. $C_{24}H_{21}NO_5S_2$ Requires: C, 61.65; H, 4.53; N, 3.00.
42		mixture of diastereoisomers **LRMS** (Thermospray): 452.4 (MH^+). **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.39 (t, 3H), 1.65 (pair of d, 3H), 4.40 (m, 2H), 5.37 (q, 1H), 6.97 (d, 1H), 7.10 (d, 1H), 7.24 (m, 1H), 7.33-7.44 (m, 3H), 7.65 (m, 1H), 7.83 (d, 2H), 8.50 (m, 1H), 8.60 (m, 2H). $C_{24}H_{21}NO_4S_2$

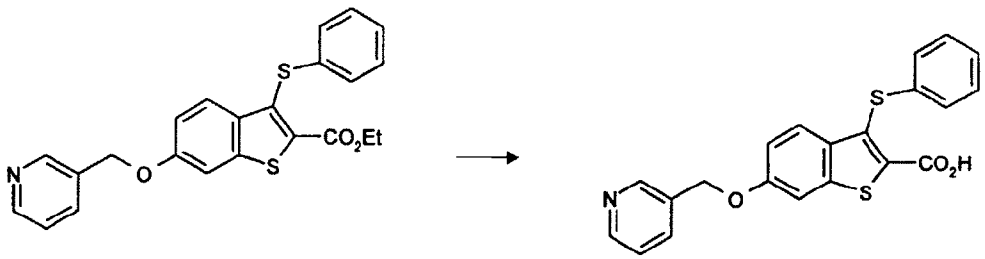
43		**LRMS** (Thermospray): 439.8 (MH^+). **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.40 (t, 3H), 4.40 (m, 2H), 5.23 (s, 2H), 7.07 (d, 1H), 7.30 (s, 1H), 7.36-7.43 (m, 3H), 7.83 (d, 2H), 8.53 (s, 1H), 8.54 (s, 1H), 8.67 (d, 1H), 8.77 (s, 1H). $C_{22}H_{18}N_2O_4S_2$.
44		**LRMS** (Thermospray): 439.7 (MH^+). **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.40 (t, 3H), 4.40 (m, 2H), 5.43 (s, 2H), 7.05 (d, 1H), 7.28-7.50 (m, 5H), 7.65 (d, 1H), 7.83 (d, 2H), 8.66 (d, 1H), 9.10 (s, 1H). $C_{22}H_{18}N_2O_4S_2$.
45		**m.p.** 155°C (from diisopropyl ether) **LRMS** (APCI): 439.5 (MH^+). **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.40 (t, 3H), 4.42 (m, 2H), 5.08 (s, 2H), 7.03 (d, 1H), 7.27 (s, 1H), 7.35-7.45 (m, 3H), 7.86 (d, 2H), 8.70 (d, 1H), 8.80 (s, 2H), 9.20 (s, 1H). $C_{22}H_{18}N_2O_4S_2$.
46		**LRMS** (Thermospray): 439.4 (MH^-). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 1.36 (t, 3H), 4.41 (q, 2H), 5.30 (s, 2H), 7.20 (d, 1H), 7.44-7.58 (m, 3H), 7.70 (d, 1H), 7.80 (m, 3H), 8.53 (d, 1H), 9.21 (d, 1H), 9.32 (s, 1H). **Analysis:** Found: C, 59.73; H, 4.11; N, 6.26. $C_{22}H_{18}N_2O_4S_2$; Requires: C, 60.26; H, 4.14; N, 6.39.
47		**m.p.** 149-151°C (from diisopropyl ether) **LRMS** (Thermospray): 455.0 (MH^+). **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 4.46 (q, 2H), 5.11 (s, 2H), 7.00-7.50 (m, 9H), 7.90 (d, 2H), 8.70 (d, 1H). **Analysis:** Found: C, 63.43; H, 4.16. $C_{24}H_{19}FO_4S_2$; Requires: C, 63.42; H, 4.21.
48		**LRMS** (Thermospray): 480.9 (MH^+). **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.42 (t, 3H), 4.45 (m, 2H), 5.00 (s, 2H), 5.98 (s, 2H), 6.79-6.83 (m, 3H), 7.04 (d, 1H), 7.30 (s, 1H), 7.40-7.53 (m, 3H), 7.89 (d, 2H), 8.68 (d, 1H). $C_{25}H_{20}O_6S_2$
49		**m.p.** 175-177°C (from diisopropyl ether) **LRMS** (Thermospray): 462.0 (MH^+). **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 4.46 (q, 2H), 5.15 (s, 2H), 7.06 (dd, 1H), 7.28 (1H, obscured by $CDCl_3$), 7.40-7.53 (m, 4H), 7.65 (m, 2H), 7.73 (s, 1H), 7.90 (d, 2H), 8.73 (d, 1H).

		Analysis: Found: C, 64.65; H, 4.08; N, 3.06. $C_{25}H_{19}NO_4S_2$; Requires: C, 65.05; H, 4.15; N, 3.04.
50		**m.p.** 127°C (from diisopropyl ether) **LRMS** (Thermospray): 443.0 (MH^+). **^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.43 (t, 3H), 4.44 (q, 2H), 5.13 (s, 2H), 7.05 (dd, 1H), 7.13 (d, 1H), 7.23-7.50 (m, 6H), 7.80 (d, 2H), 8.68 (d, 1H). $C_{22}H_{18}O_4S_3$
51		**m.p.** 142°C (from diisopropyl ether) **LRMS** (Thermospray): 444.3 (MH^+). **^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.43 (t, 3H), 4.43 (m, 2H), 5.34 (s, 2H), 7.05 (dd, 1H), 7.33 (s, 1H), 7.40-7.50 (m, 3H), 7.85-7.95 (m, 3H), 8.70 (d, 1H), 8.83 (s, 1H). $C_{21}H_{17}NO_4S_3$.

Example 52

3-(Phenylsulfanyl)-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylic acid

[0130]



[0131] Sodium hydroxide (0.5ml of 2M in water) was added to a solution of ethyl 3-(phenylsulfanyl)-6-(3 -pyridylmethoxy)benzo[*b*]thiophene-2-carboxylate (Example 1, 190mg, 0.45mmol) in 1,4-dioxane, and the mixture heated to 60°C for 4 hours. The solvents were removed under reduced pressure, and the residue was dissolved in water (15ml) and washed with ethyl acetate (25ml). The aqueous layer was separated and acidified by dropwise addition of acetic acid until a white solid precipitated. The solid was isolated by filtration and dried under vacuo to give the title compound as a colourless solid (140mg).

m.p. 236-238°C

^{1}H NMR (300MHz, DMSO-d_6): δ = 5.20 (s, 2H), 7.04-7.28 (m, 6H), 7.40 (dd, 1H), 7.55 (d, 1H), 7.78 (d, 1H), 7.88 (d, 1H), 8.53 (d, 1H), 8.66 (s, 1H), 13.5 (brs, 1H).

Analysis: Found: C, 63.89; H, 3.82; N, 3.46.

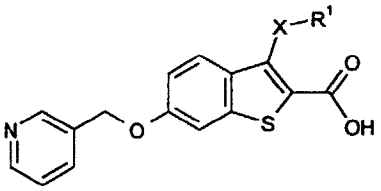
$C_{21}H_{15}NO_3S_2$ Requires: C, 64.10; H, 3.84; N, 3.56.

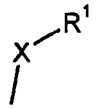
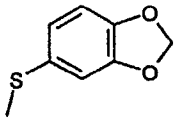
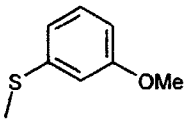
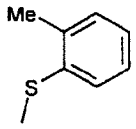
Examples 53-95

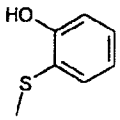
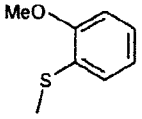
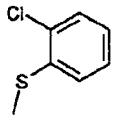
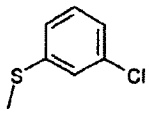
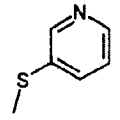
[0132] These were prepared by the method of Example 52, using the appropriate substituted benzo[*b*]thiophene-2-carboxylate esters as described earlier. Some of the Examples used methanol in place of, or in addition to, 1,4-dioxane as solvent.

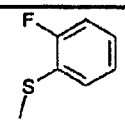
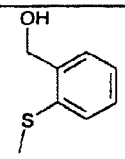
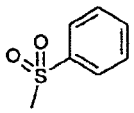
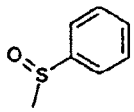
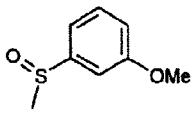
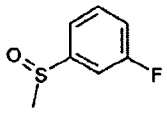
Their physical data are shown in Tables 8, 9, 10, 11, 12 and 13.

Table 8



Example N°		Physical Data
53		**m.p.** 226-228°C **LRMS** (APCI): 437.8 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.22 (s, 2H), 5.97 (s, 2H), 6.80 (m, 3H), 7.10 (dd, 1H), 7.40 (dd, 1H), 7.62 (d, 1H), 7.72 (s, 1H), 7.86 (d, 1H), 8.54 (d, 1H), 8.67 (s, 1H). $C_{22}H_{15}NO_5S_2$.
54		**m.p.** 210-214°C **LRMS** (APCI): 380.2 (MH^+-CO_2), 423.7 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.64 (s, 3H), 5.21 (s, 2H), 6.60 (d, 1H), 6.66 (s, 1H), 6.72 (d, 1H), 7.07-7.18 (m, 2H), 7.40 (dd, 1H), 7.56 (d, 1H), 7.78 (s, 1H), 7.88 (d, 1H), 8.53 (d, 1H), 8.67 (s, 1H). **Analysis:** Found: C, 61.49; H, 3.94; N, 3.32. $C_{22}H_{17}NO_4S_2$; 1/4 H_2O Requires: C, 61.74; H, 4.12; N, 3.27.
55		**m.p.** 250-251°C **^{1}H NMR** (300MHz, DMSO-d_6): δ = 2.38 (s, 3H), 5.20 (s, 2H), 6.70 (d, 1H), 6.93-7.13 (m, 3H), 7.21 (d, 1H), 7.39-7.45 (m, 2H), 7.78 (s, 1H), 7.88 (d, 1H), 8.54 (d, 1H), 8.67 (s, 1H). **Analysis:** Found: C, 64.26; H, 4.24; N, 3.41.

		$C_{22}H_{17}NO_3S_2$; 1/5 H_2O Requires: C, 64.28; H, 4.27; N, 3.41.
56		**m.p.** 261-263°C **LRMS** (APCI): 366.1 (MH^+-CO_2), 409.7 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.19 (s, 2H), 6.60 (m, 2H), 6.80 (d, 1H), 6.92-7.08 (m, 2H), 7.42 (dd, 1H), 7.52 (d, 1H), 7.73 (s, 1H), 7.87 (d, 1H), 8.55 (d, 1H), 8.67 (s, 1H).. **Analysis:** Found: C, 60.05; H, 3.65; N, 3.27. $C_{21}H_{15}NO_4S_2$; 1/2 H_2O Requires: C, 60.27; H, 3.85; N, 3.35.
57		**m.p.** 215-216°C **LRMS** (Thermospray): 379.7 (MH^+-CO_2), 423.6 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.85 (s, 3H), 5.22 (s, 2H), 6.46 (d, 1H), 6.71 (dd, 1H), 7.00 (d, 1H), 7.05-7.15 (m, 2H), 7.41 (dd, 1H), 7.50 (d, 1H), 7.79 (s, 1H), 7.88 (d, 1H), 8.55 (d, 1H), 7.68 (s, 1H), 13.5 (brs, 1H). **Analysis:** Found: C, 60.70; H, 4.35; N, 3.03. $C_{22}H_{17}NO_4S_2$; 1/2 H_2O Requires: C, 61.09; H, 4.20; N, 3.24.
58		**m.p.** 220-222°C **LRMS** (Thermospray): 384.3 (MH^+-CO_2), 428.0 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.22 (s, 2H), 6.58 (d, 1H), 7.05-7.18 (m, 3H), 7.40-7.56 (m, 3H), 7.82 (s, 1H), 7.90 (d, 1H), 8.54 (d, 1H), 8.69 (s, 1H), 13.53 (brs, 1H). **Analysis:** Found: C, 58.41; H, 3.33; N, 3.26. $C_{21}H_{14}ClNO_3S_2$ Requires: C, 58.94; H, 3.30; N, 3.27.
59		**m.p.** 237-238°C **LRMS** (Thermospray): 384.3 (MH^+-CO_2), 428.0 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.22 (s, 2H), 7.00 (d, 1H), 7.10-7.30 (m, 4H), 7.40 (dd, 1H), 7.60 (d, 1H), 7.80 (s, 1H), 7.89 (d, 1H), 8.54 (d, 1H), 8.68 (s, 1H), 13.65 (brs, 1H). **Analysis:** Found: C, 58.54; H, 3.38; N, 3.08. $C_{21}H_{14}ClNO_3S_2$ Requires: C, 58.94; H, 3.30; N, 3.27.
60		**m.p.** 227-229°C **LRMS** (Thermospray): 351.3 (MH^+-CO_2), 395.0 (MH^-) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.22 (s, 2H), 7.13 (d, 1H), 7.26 (dd, 1H), 7.40-7.50 (m, 2H), 7.62 (d, 1H), 7.81 (s, 1H), 7.90 (d, 1H), 8.36 (d, 1H), 8.39 (s, 1H), 8.55 (d, 1H), 8.70 (s, 1H), 13.70 (brs, 1H). $C_{20}H_{14}N_2O_3S_2$
61		**m.p.** 241-242°C **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.19 (s, 2H), 6.84 (dd, 1H), 7.00

		(m, 1H), 7.08 (dd, 1H), 7.16-7.23 (m, 2H), 7.38 (m, 1H), 7.52 (d, 1H), 7.76 (s, 1H), 7.84 (d, 1H), 8.50 (d, 1H), 8.65 (s, 1H). $C_{21}H_{14}FNO_3S_2$
62		**m.p.** 248°C **LRMS** (Thermospray): 380.2 (MH^+-CO_2), 424.3 (MH^+). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 4.65 (s, 2H), 5.21 (s, 2H), 5.35 (brs, 1H), 6.76 (d, 1H), 7.05 (m, 2H), 7.18 (t, 1H), 7.40-7.50 (m, 3H), 7.76 (s, 1H), 7.88 (d, 1H), 8.55 (d, 1H), 8.68 (s, 1H). $C_{22}H_{17}NO_4S_2$
63		**m.p.** 218-220°C **LRMS** (Thermospray): 381.8 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.21 (s, 2H), 7.28 (d, 1H), 7.42 (dd, 1H), 7.58-7.73 (m, 3H), 7.80-7.92 (m, 2H), 8.13 (d, 2H), 8.27 (d, 1H), 8.56 (d, 1H), 8.68 (s, 1H), 14.4 (brs, 1H). **Analysis:** Found: C, 59.26; H, 3.57; N, 3.18. $C_{21}H_{15}NO_5S_2$ Requires: C, 59.28; H, 3.55; N, 3.29.
64		**m.p.** 260-263°C **LRMS** (Thermospray): 366.1 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.20 (s, 2H), 7.10 (d, 1H), 7.38-7.57 (m, 4H), 7.70-7.80 (m, 3H), 7.86 (d, 1H), 8.47 (d, 1H), 8.53 (d, 1H), 8.66 (s, 1H), 14.2 (brs, 1H). **Analysis:** Found: C, 61.27; H, 3.64; N, 3.34. $C_{21}H_{15}NO_4S_2$ Requires: C, 61.59; H, 3.69; N, 3.42.
65		**m.p.** 239-241°C **LRMS** (Thermospray): 396.2 (MH^+-CO_2) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.75 (s, 3H), 5.20 (s. 2H), 7.00 (dd, 1H), 7.13 (dd, 1H), 7.25-7.45 (m, 4H), 7.78 (s, 1H), 7.86 (d, 1H), 8.49 (d, 1H), 8.53 (d, 1H), 8.66 (s, 1H). **Analysis:** Found: C, 59.44; H, 3.83; N, 3.06. $C_{22}H_{17}NO_5S_2$ Requires: C, 60.44; H, 3.90; N, 3.19.
66		**m.p.** 156°C **LRMS** (Thermospray): 384.2 (MH^+-CO_2). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.18 (s, 2H), 7.10 (d, 1H), 7.27 (dd, 1H), 7.38 (m, 1H), 7.50-7.60 (m, 3H), 7.76 (s, 1H), 7.82 (d, 1H), 8.40 (d, 1H), 8.50 (d, 1H), 8.63 (s, 1H). $C_{21}H_{14}FNO_4S_2$.
		m.p. 238°C **LRMS** (Thermospray): 384.2 (MH^+-CO_2).

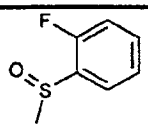
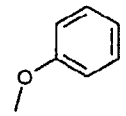
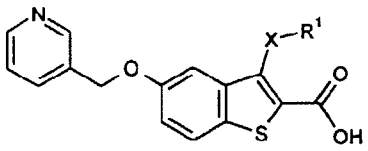
67		**^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.18 (s, 2H), 7.08 (dd, 1H), 7.21 (dd, 1H), 7.33-7.40 (m, 2H), 7.50 (m, 1H), 7.72-7.85 (m, 3H), 8.34 (d, 1H), 8.50 (d, 1H), 8.63 (s, 1H). $C_{21}H_{14}FNO_4S_2$.
68		**m.p.** 248-250°C **LRMS** (Thermospray): 333.8 (MH^+-CO_2), 378.2 (MH^+). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.23 (s, 2H), 6.90 (d, 2H), 7.00-7.13 (m, 2H), 7.23-7.46 (m, 4H), 7.76 (s, 1H), 7.90 (d, 1H), 8.55 (d, 1H), 8.70 (s, 1H), 13.2 (brs, 1H). $C_{21}H_{15}NO_4S$

Table 9



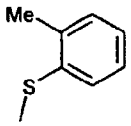
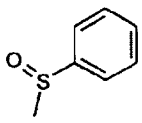
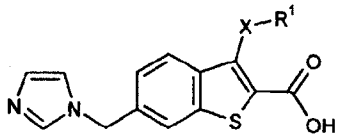
Example N°		Physical Data
69		**m.p.** 235°C **LRMS** (Thermospray): 364.1 (MH^+-CO_2) **^{1}H NMR** (400MHz, DMSO-d_6): δ = 2.39 (s, 3H), 4.94 (s, 2H), 6.70 (d, 1H), 6.90-7.06 (m, 3H), 7.13 (d, 1H), 7.19 (d, 1H), 7.36 (dd, 1H), 7.72 (d, 1H), 7.85 (d, 1H), 8.50 (d, 1H), 8.56 (s, 1H). $C_{22}H_{17}NO_3S_2$
70		**m.p.** 245°C **LRMS** (Thermospray): 366.1 (MH^+-CO_2) **^{1}H NMR** (400MHz, DMSO-d_6): δ = [5.08 (d, 1H), 5.09 (d, 1H) non-equivalent OCH_2Py^3], 7.28 (d, 1H), 7.40-7.55 (m, 4H), 7.78 (d, 2H), 7.88 (d, 1H), 8.00 (d, 1H), 8.15 (s, 1H), 8.56 (d, 1H), 8.69 (s, 1H). **Analysis:** Found: C, 59.88; H, 3.49; N, 3.23. $C_{21}H_{15}NO_4S_2$; 1/2 H_2O Requires: C, 60.27; H, 3.85; N, 3.35.

Table 10



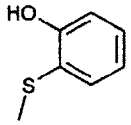
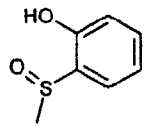
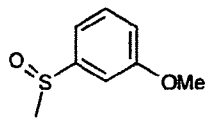
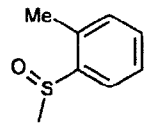
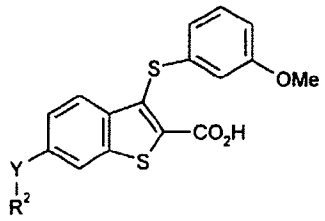
Example N°		Physical Data
71		**m.p.** 168-170°C **LRMS** (Thermospray): 339.6 (MH^+-CO_2), 383.3 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.33 (s, 2H), 6.60 (t, 1H), 6.74 (d, 1H), 6.95-7.05 (m, 2H), 7.15 (s, 1H), 7.30 (d, 1H), 7.39 (s, 1H), 7.77 (d, 1H), 7.90 (s, 1H), 8.25 (s, 1H). **Analysis**: Found: C, 57.27; H, 3.77; N, 7.00. $C_{19}H_{14}N_2O_3S_2$; H_2O Requires: C, 56.98; H, 4.03; N, 6.99.
72		**m.p.** 235-238°C **HRMS** (+ve ion electrospray): 399.0 (MH^+) **^{1}H NMR** (300MHz, DMSO-d_6 + drop TFA-d): δ = 5.51 (s, 2H), 6.73 (d, 1H), 6.99 (t, 1H), 7.22 (t, 1H), 7.36 (d, 1H), 7.62 (s, 1H), 7.74 (s, 1H), 7.82 (d, 1H), 8.03 (s, 1H), 8.36 (d, 1H), 9.22 (s, 1H). **Analysis**: Found: C, 55.99; H, 3.56; N, 6.76. $C_{19}H_{14}NO_4S_2$; 1/2 H_2O; Requires: C, 56.00; H, 3.71; N, 6.88.
73		**LRMS** (Thermospray): 369.2 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6 + drop TFA-d): δ = 3.73 (s, 3H), 5.53 (s, 2H), 6.99 (d, 1H), 7.28-7.48 (m, 4H), 7.65 (s, 1H), 7.75 (s, 1H), 8.08 (s, 1H), 8.60 (d, 1H), 9.22 (s, 1H). **Analysis**: Found: C, 57.05; H, 3.80; N, 6.61. $C_{20}H_{16}N_2O_4S_2$; 1/2 H_2O Requires: C, 56.99; H, 4.06; N, 6.65.
74		**m.p.** 224-226°C **LRMS** (Thermospray): 353.3 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6 + drop TFA-d): δ = 2.33 (s, 3H), 5.53 (s, 2H), 7.21 (m, 1H), 7.30-7.43 (m, 3H), 7.63 (s, 1H), 7.75 (s, 1H), 7.81 (dd, 1H), 8.10 (s, 1H), 8.52 (d, 1H), 9.22 (s, 1H). **Analysis**: Found: C, 59.68; H, 4.00; N, 6.87. $C_{20}H_{16}N_2O_3S_2$; 1/4 H_2O Requires: C, 59.90; H, 4.14; N, 6.99.

Table 11



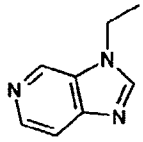
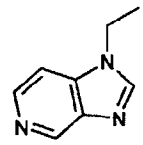
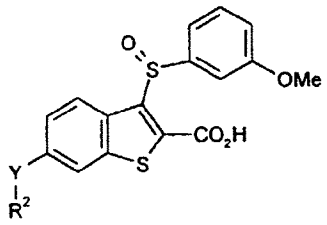
Example N°	Y, R^2	Physical Data
75		**m.p.** >270°C **LRMS** (APCI): 404.2 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.62 (s, 3H), 5.72 (s, 2H), 6.59 (d, 1H), 6.67 (s, 1H), 6.70 (d, 1H), 7.10 (t, 1H), 7.40 (d, 1H), 7.63-7.70 (m, 2H), 8.13 (s, 1H), 8.30 (d, 1H), 8.63 (s, 1H), 8.92 (s, 1H). $C_{23}H_{17}N_3O_3S_2$
76		**m.p.** 160-162°C **LRMS** (APCI): 404.2 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.61 (s, 3H), 5.63 (s, 2H), 6.58 (d, 1H), 6.65 (s, 1H), 6.69 (d, 1H), 7.10 (t, 1H), 7.34 (d, 1H), 7.59-7.65 (m, 2H), 8.02 (s, 1H), 8.29 (d, 1H), 8.57 (s, 1H), 8.93 (s, 1H). $C_{23}H_{17}N_3O_3S_2$

Table 12



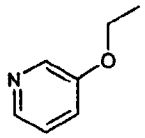
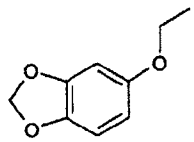
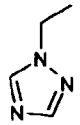
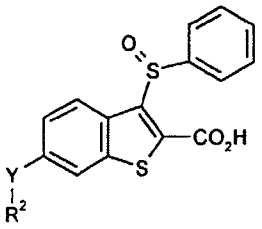
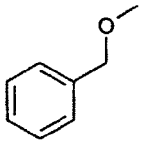
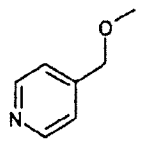
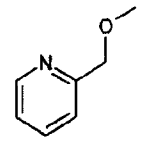
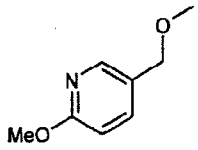
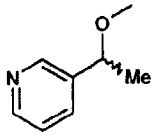
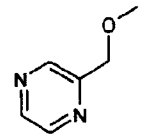
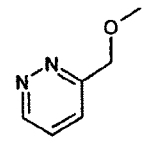
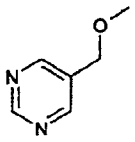
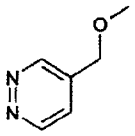
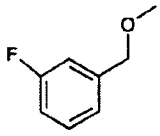
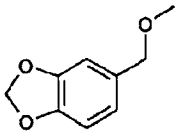
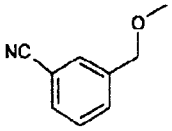
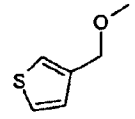
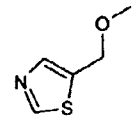
Example N°		Physical Data
77		**m.p.** 224-226°C **LRMS** (Thermospray): 396.3 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.77 (s, 3H), 5.28 (s, 2H), 7.01 (dd, 1H), 7.27-7.55 (m, 6H), 8.15-8.20 (m, 2H), 8.36 (d, 1H), 8.60 (d, 1H). $C_{22}H_{17}NO_5S_2$
78		**m.p.** 85-88°C **LRMS** (Thermospray): 439.1 (MH^+-CO_2), 482.6 (MH^+). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.77 (s, 3H), 5.10 (s, 2H), 5.93 (s, 2H), 6.42 (dd, 1H), 6.70 (s, 1H), 6.78 (d, 1H), 7.02 (d, 1H), 7.30-7.52 (m, 4H), 8.15 (s, 1H), 8.58 (d, 1H), 14.5 (brs, 1H). **Analysis:** Found: C, 58.39; H, 3.66; N, nil. $C_{24}H_{18}O_7S_2$; 1/2 H_2O Requires: C, 58.64; H, 3.90; N, nil.
79		**m.p.** 249-251°C **LRMS** (Thermospray): 370.0 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.77 (s, 3H), 5.50 (s, 2H), 7.00 (d, 1H), 7.30-7.45 (m, 4H), 7.92 (s, 1H), 7.98 (s, 1H), 8.55 (d, 1H), 8.62 (s, 1H). **Analysis:** Found: C, 54.79; H, 3.28; N, 9.93. $C_{19}H_{15}N_3O_4S_2$; Requires: C, 55.19; H, 3.66; N, 10.17.

Table 13



Example N°		Physical Data
80		**m.p.** 206-208°C (recrystallised from diethyl ether) **LRMS** (Thermospray): 365.0 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.16 (s, 2H), 7.10 (d, 1H), 7.28-7.60 (m, 8H), 7.70-7.88 (m, 3H), 8.48 (d, 1H). **Analysis**: Found: C, 64.08; H, 3.88; N, nil.

		$C_{22}H_{16}O_4S_2$; Requires: C, 64.68; H, 3.95; N, nil.
81		**m.p.** >260°C **LRMS** (Thermospray): 366.1 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6 + drop TFA-d): δ = 5.57 (s, 2H), 7.20 (dd, 1H), 7.40-7.55 (m, 3H), 7.71 (s, 1H), 7.79 (d, 2H),.8.08 (d, 2H), 8.54 (d, 1H), 8.91 (d, 2H). **Analysis:** Found: C, 61.22; H, 3.67; N, 3.33. $C_{21}H_{15}NO_4S_2$; Requires: C, 61.59; H, 3.69; N, 3.42.
82		**m.p.** 132-134°C **LRMS** (Thermospray): 366.3 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.22 (s, 2H), 7.15 (dd, 1H), 7.32 (m, 1H), 7.42-7.57 (m, 4H), 7.70-7.86 (m, 4H), 8.47 (d, 1H), 8.56 (d, 1H). $C_{21}H_{15}NO_4S_2$
83		**m.p.** 189-191°C **LRMS** (Thermospray): 440.0 (MH+), 396.1 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 3.85(s, 3H), 5.08 (s, 2H), 6.82 (d, 1H), 7.10 (d, 1H), 7.43-7.58 (m, 3H), 7.73-7.85 (m, 4H), 8.28 (s, 1H), 8.48 (d, 1H). $C_{22}H_{17}NO_5S_2$
85		mixture of diastereoisomers **LRMS** (Thermospray): 380.1 (MH^+-CO_2), 424.0 (MH^+). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 1.60 (pair of d, 3H), 5.68 (q, 1H), 7.09 (dd, 1H), 7.35 (m, 1H), 7.40-7.57 (m, 3H), 7.63 (m, 1H), 7.70-7.82 (m, 3H), 8.40-8.50 (m, 2H), 8.66 (s, 1H). $C_{22}H_{17}NO_4S_2$
86		**m.p.** 135-136°C **LRMS** (Thermospray): 366.7 (MH^+-CO_2). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.28 (s, 2H), 7.14 (d, 1H), 7.40-7.53 (m, 3H), 7.72-7.79 (m, 3H), 8.43 (d, 1H), 8.59 (s, 1H), 8.61 (s, 1H), 8.78 (s, 1H). $C_{20}H_{14}N_2O_4S_2$
87		**m.p.** 237-238°C **LRMS** (Thermospray): 367.6 (MH^+-CO_2). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.42 (s, 2H), 7.13 (d, 1H), 7.40-7.53 (m, 3H), 7.65-7.80 (m, 5H), 8.44 (d, 1H), 9.17 (d, 1H). $C_{20}H_{14}N_2O_4S_2$

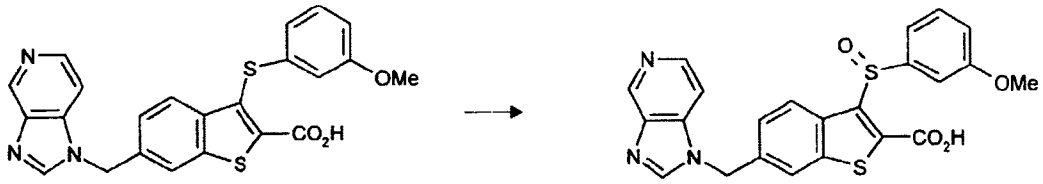
87		**m.p.** 251-252°C **LRMS** (APCI): 367.3 (MH^+-CO_2). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.19 (s, 2H), 7.18 (dd, 1H), 7.40-7.52 (m, 3H), 7.70-7.80 (m, 3H), 8.43 (d, 1H), 8.88 (s, 2H), 9.13 (s, 1H). $C_{20}H_{14}N_2O_4S_2$
88		**m.p.** 237-239°C **LRMS** (Thermospray): 367.1 (MH^+-CO_2). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.29 (s, 2H), 7.18 (d, 1H), 7.42-7.55 (m, 3H), 7.64-7.80 (m, 4H), 8.50 (d, 1H), 9.20 (d, 1H), 9.28 (s, 1H). $C_{20}H_{14}N_2O_4S_2$
89		**m.p.** 206-208°C **LRMS** (Thermospray): 383.1 (MH^+-CO_2), 427.1 (MH^+). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.18 (s, 2H), 7.12 (m, 2H), 7.27 (d, 2H), 7.39-7.57 (m, 4H), 7.75 (s, 1H), 7.80 (d, 2H), 8.49 (d, 1H), 14.3 (brs, 1H). **Analysis:** Found: C, 61.64; H, 3.46. $C_{22}H_{15}FO_4S_2$; Requires: C, 61.96; H, 3.55.
90		**m.p.** 185-186°C **LRMS** (Thermospray): 409.3 (MH^+-CO_2), 452.8 (MH^+). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.01 (s, 2H), 5.98 (s, 2H), 6.85-6.95 (m, 2H), 6.99 (s, 1H), 7.05 (d, 1H), 7.40-7.55 (m, 3H), 7.68 (s, 1H), 7.80 (d, 2H), 8.43 (d, 1H). $C_{23}H_{16}O_6S_2$
91		**m.p.** 230-232°C **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.20 (s, 2H), 7.13 (d, 1H), 7.43-7.62 (m, 4H), 7.72-7.82 (m, 5H), 7.93 (s, 1H), 8.50 (d, 1H). **Analysis:** Found: C, 63.58; H, 3.66; N, 3.05. $C_{23}H_{15}NO_4S_2$; Requires: C, 63.72; H, 3.49. N, 3.23
92		**m.p.** 110°C **LRMS** (Thermospray): 371.1 (MH^+-CO_2). **^{1}H NMR** (300MHz, DMSO-d_6): δ = 5.15 (s, 2H), 7.08 (d, 1H), 7.16 (d, 1H), 7.43-7.60 (m, 5H), 7.72-7.85 (m, 3H), 8.46 (d, 1H). $C_{20}H_{14}O_4S_3$.
93		**m.p.** 244°C **LRMS** (Thermospray): 372.3 (MH^+-CO_2), 416.8 (MH^+). **^{1}H NMR** (400MHz, DMSO-d_6): δ = 5.44 (s, 2H), 7.10 (dd, 1H),

		7.43-7.57 (m, 3H), 7.76-7.83 (m, 3H), 8.02 (s, 1H), 8.49 (d, 1H), 9.10 (s, 1H). $C_{19}H_{13}NO_4S_3$.

Example 94

6-(1*H*-Imidazo[4,5-*c*]pyridin-1-ylmethyl)-3-[(3-methoxyphenyl)sulfinyl] benzo[*b*]thiophene-2-carboxylic acid

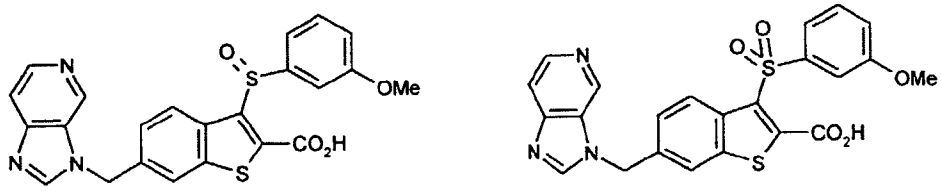
[0133]



[0134] Hydrogen peroxide in water (0.07ml of 30%w/v, 0.58mmol) was added to a mixture of 6-(1*H*-Imidazo[4,5-*c*] pyridin-1-ylmethyl)-3-[(3-methoxyphenyl)sulfanyl]benzo[*b*]thiophene-2-carboxylic acid (Example 23 - 218mg, 0.49mmol) in acetic acid (2ml), and 2M hydrochloric acid (2ml). The solution was heated to 100°C for 1 hour. The solution was cooled and the solvents were evaporated under reduced pressure. The residue was dissolved in a hot mixture of aqueous sodium hydroxide (5ml of 1M) and methanol (5ml). After acidifying the solution with acetic acid, and cooling, the precipitate was collected by filtration to give the title compound as a colourless solid (95mg).
LRMS (Thermospray): 420.2 (MH^+-CO_2)
^{1}H NMR (300MHz, DMSO-d_6): δ = 3.73 (s, 3H), 5.65 (s, 2H), 6.98 (d, 1H), 7.30-7.45 (m, 4H), 7.71 (d, 1H), 8.01 (s, 1H), 8.36 (d, 1H), 8.53 (d, 1H), 8.64 (s, 1H), 9.05 (s, 1H).
$C_{23}H_{17}N_3O_4S_2$

Example 95 & 96

[0135]



6-(3*H*-Imidazo[4,5-*c*]pyridin-3-ylmethyl)-3-[(3-methoxyphenyl)sulfinyl] benzo[*b*]thiophene-2-carboxylate &

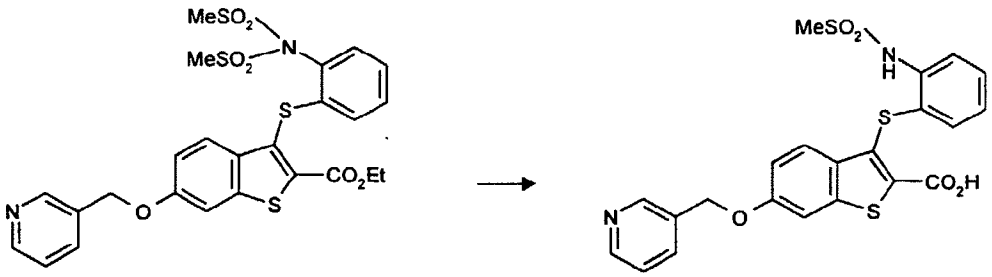
6-(3*H*-Imidazo[4,5-*c*]pyridin-3-ylmethyl)-3-[(3-methoxyphenyl)sulfonyl] benzo[*b*]thiophene-2-carboxylate

[0136] The title compounds were prepared from the compound of Example 22 using the method of Example 94, as a colourless solid comprising a 1:1 mixture of sulfinyl (Example 95) and sulfonyl (Example 96) analogues.
LRMS (APCI): 419.9 (sulfinyl M^+ -CO_2), 436.2 (sulfonyl M^+-CO_2)
$C_{23}H_{17}N_3O_4S_2$ & $C_{23}H_{17}N_3O_5S_2$

Example 97

3-[2-(Methylsulfonylamino)phenyl]sulfanyl-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylic acid

[0137]



[0138] Sodium hydroxide (1ml of 1M in water) was added to a solution of ethyl 3-[2-(*N,N*-dimethylsulfonylamino) phenyl]sulfanyl-6-(3-pyridylmethoxy) benzo[*b*]thiophene-2-carboxylate (Example 16 - 185mg, 0.31 mmol) in methanol (5ml), and the solution was heated at reflux for 40 minutes. The hot solution was acidified by dropwise addition of acetic acid, diluted with water (5ml), and cooled. The solid precipitate was isolated by filtration and dried under vacuo to give the title compound as a colourless solid (102mg).

m.p. 258-260°C

LRMS (Thermospray): 487.4 (MH^+), 442.8 ($MH^+ - CO_2$).

^{1}H NMR (300MHz, DMSO-d_6): δ = 3.08 (s, 3H), 5.20 (s, 2H), 6.72 (d, 1H), 6.99-7.13 (m. 2H), 7.18 (t, 1H), 7.35 (d, 1H), 7.40 (dd, 1H), 7.59 (d, 1H), 7.78 (s, 1H), 7.87 (d, 1H), 8.54 (d, 1H), 8.67 (s, 1H), 9.48 (s, 1H), 13.60 (brs, 1H).

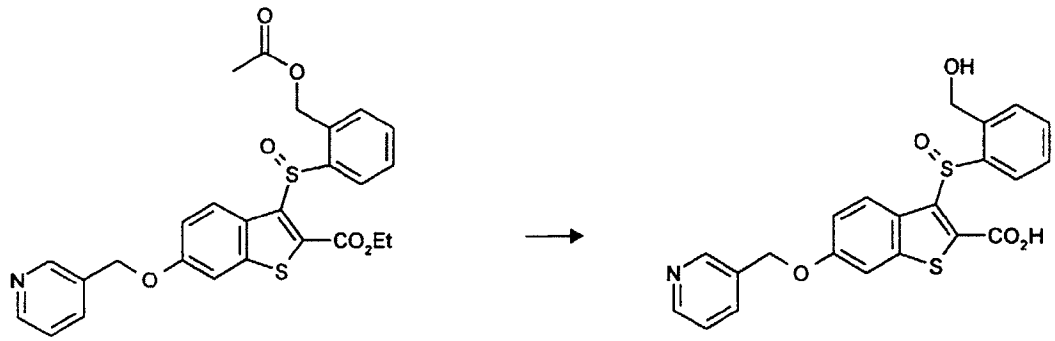
Analysis: Found: C, 53.81; H, 3.73; N, 5.58.

$C_{22}H_{18}N_2O_5S_3$ Requires: C, 54.30; H, 3.73; N, 5.76.

Example 98

3-[2-(Hydroxymethyl)phenylsulfinyl]-6-(3-pyridylmethoxy)benzo[*b*]thiophene-2-carboxylic acid

[0139]



[0140] Sodium hydroxide (3ml of 1M in water) was added to a suspension of ethyl 3-(2-[(methylcarbonyloxy)methyl] phenylsulfinyl)-6-(3-pyridylmethoxy)benzo [*b*]thiophene-2-carboxylate (Example 35 - 500mg, 0.98mmol) in methanol (15ml). The mixture was heated to reflux for 30 minutes. The resultant solution was cooled, diluted with water and acidified by dropwise addition of acetic acid. The precipitate was isolated by filtration and washing with water. The solid was recrystallised twice by dissolving in hot methanol, and cooling, to give the title compound as a colourless solid (71mg).

m.p. 210°C

LRMS (Thermospray): 395.7 ($MH^+ - CO_2$).

^{1}H NMR (400MHz, DMSO-d_6): δ = [4.42 (d, 1H) & 4.78 (d, 1H) non-equivalent $\underline{CH_2}OH$], 5.21 (s, 2H), 5.40 (brs, 1H), 7.13 (d, 1H), 7.40-7.60 (m, 4H), 7.77-7.82 (m, 2H), 7.90 (d, 1H), 8.44 (d, 1H), 8.56 (d, 1H), 8.70 (s, 1H).

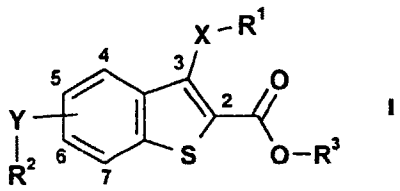
$C_{22}H_{17}NO_5S_2$

Example 99

[0141] The compounds of Examples 56 and 71 were tested in Test B above using rat aorta, and found to have pA_2 values of 7.83 and 6.64 respectively.

Claims

1. A compound of formula I,



I

wherein

X represents O or $S(O)_m$;
R^1 and R^2 independently represent phenyl, naphthyl or heteroaryl containing 1, 2 or 3 heteroatoms independently selected from N, S and O; the ring being optionally fused to a saturated or unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms independently selected from N, S and O; the ring system as a whole being optionally substituted by one or more groups selected from OH, halogen, CN, NH_2, $(CH_3SO_2)HN$, $(CH_3SO_2)_2N$, C_{1-6} alkyl (optionally substituted by OH or CH_3CO_2) and C_{1-6} alkoxy;
Y represents a bond, O, $(CH_2)_n$, $O(CH_2)_n$, $(CH_2)_nO$, or $CH(C_{1-6}$ alkyl)O;
R^3 represents H or C_{1-6} alkyl;
m represents 0, 1, or 2; and
n represents 1, or 2;

provided that:

(i) when R^2 is linked to Y via a nitrogen atom, then Y does not represent O, $O(CH_2)_n$ or CH_2O; and
(ii) when R^3 represents H, then neither R^1 nor R^2 is substituted by $(CH_3SO_2)_2N$; or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein X represents SO or S.

3. A compound as claimed in claim 1 or claim 2, wherein R^1 represents phenyl or substituted phenyl.

4. A compound as claimed in any one of the preceding claims, wherein R^2 represents 3-pyridyl, 5-pyrimidinyl, 1-imidazolyl, imidazo[4,5-c]pyridin-3-yl or 3-thienyl.

5. A compound as claimed in any one of the preceding claims, wherein Y represents CH_2, CH_2O or OCH_2.

6. A compound as claimed in any one of the preceding claims, wherein Y is attached to the 6-position of the benzothiophene ring.

7. A compound as claimed in any one of the preceding claims, wherein R^3 represents H.

8. A compound as claimed in any one of the preceding claims, wherein a heteroatom in R^2 is separated from the benzothiophene ring by 4 atoms.

9. A compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

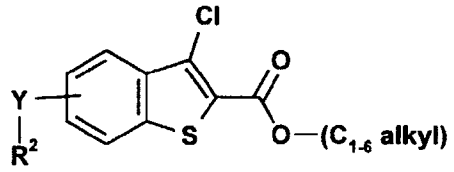
10. A pharmaceutical formulation comprising a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

11. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, male erectile dysfunction, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia or cyclosporin induced nephrotoxicity.

12. A method of treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, male erectile dysfunction, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia or cyclosporin induced nephrotoxicity, which comprises administering a therapeutically effective amount of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.

13. A process for the production of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolysis of a compound of formula I in which R^3 represents C_{1-6} alkyl, to produce a corresponding compound of formula I in which R^3 represents H;
(b) oxidation of a compound of formula I in which X represents S and R^3 represents C_{1-6} alkyl, to produce a corresponding compound of formula I in which X represents SO or SO_2;
(c) when X represents S or O, reaction of a compound of formula II,

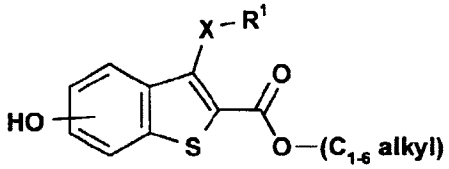


II

wherein Y and R^2 are as defined in claim 1, with a compound of formula III,

$$HX^aR^1 \qquad III$$

wherein R^1 is as defined in claim 1 and X^a represents S or O, in the presence of a base; (d) when Y represents $(CH_2)_nO$ or $CH(C_{1-6}$ alkyl)O, reaction of a compound of formula V,

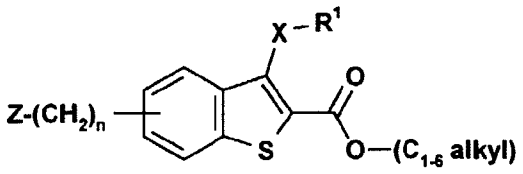


V

wherein X and R^1 are as defined in claim 1, with a compound of formula Va,

$$R^2Y^aZ \qquad Va$$

wherein R^2 is as defined in claim 1, Y^a represents $(CH_2)_n$ or $CH(C_{1-6}$ alkyl), and Z represents a leaving group or OH;
(e) when Y represents $O(CH_2)_n$, reaction of a compound of formula VII,



VII

wherein X, R^1 and n are as defined in claim 1, and Z is a leaving group, with a compound of formula VIIa,

$$R^2OH \qquad \text{VIIa}$$

wherein R^2 is as defined in claim 1, in the presence of a base;
(f) when Y represents $(CH_2)_n$ and R^2 represents N-linked heteroaryl, reaction of a compound of formula VII, as defined above, with a compound of formula VIIb,

$$R^{2a}H \qquad \text{VIIb}$$

wherein R^{2a} represents an N-containing heteroaromatic compound with a hydrogen atom attached to the N, in the presence of a base;

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable salt or vice versa.

14. Compounds of formulae V and VII, as defined in claim 13.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 98 30 9715

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	P.E. CROSS ET AL.: "Selective thromboxane synthetase inhibitors" JOURNAL OF MEDICINAL CHEMISTRY., vol. 29, no. 9, 1986, pages 1637-1643, XP002066696 WASHINGTON US * the whole document * ---	1-14	C07D333/70 C07D409/12 C07D471/04 C07D409/14 C07D417/12 A61K31/38 A61K31/44 A61K31/41 //(C07D471/04, 235:00,221:00)
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TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claim 12 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
THE HAGUE	2 March 1999	Chouly, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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